MTMT közlemény és idéző összefoglaló táblázat				
Kvell Krisztián adatai (2024.04.06)				
Közlemény típusok	**Száma**		**Hivatkozások 1**	
Tudományos közlemények	Összes	Részletezve	Független	Összes
I. Tudományos folyóiratcikk	47	---	---	---
külföldi kiadású szakfolyóiratban idegen nyelven	---	46	815	993
külföldi kiadású szakfolyóiratban magyar nyelven	---	0	0	0
hazai kiadású szakfolyóiratban idegen nyelven	---	0	0	0
hazai kiadású szakfolyóiratban magyar nyelven	---	1	0	0
II. Könyvek	0	---	---	---
a) Könyv, szerzőként	0	---	---	---
idegen nyelvű	---	0	0	0
magyar nyelvű	---	0	0	0
b) Könyv, szerkesztőként2	0	---	---	---
idegen nyelvű	---	0	---	---
magyar nyelvű	---	0	---	---
III. Könyvrészlet	4	---	---	---
idegen nyelvű	---	4	1	3
magyar nyelvű	---	0	0	0
IV. Konferenciaközlemény folyóiratban vagy konferenciakötetben	0	---	---	---
idegen nyelvű	---	0	0	0
magyar nyelvű	---	0	0	0
Közlemények összesen (I.-IV.)	51	---	816	996
Absztrakt3	41	---	1	1
Kutatási adat	0		0	0
További tudományos művek4	16	---	1	1
Összes tudományos közlemény	108	---	818	998
Hirsch index5	19	---	---	---
Oktatási művek	2	---	---	---
Felsőoktatási művek	2	---	---	---
Felsőoktatási tankönyv idegen nyelvű	---	0	0	0
Felsőoktatási tankönyv magyar nyelvű	---	1	0	0
Felsőoktatási tankönyv része idegen nyelven	---	1	0	0
Felsőoktatási tankönyv része magyar nyelven	---	0	0	0
Oktatási anyag	0	---	0	0
Oltalmi formák	0	---	0	0
Alkotás	0	---	0	0
Ismeretterjesztő művek	0	---	---	---
Folyóiratcikk		0	0	0
Könyvek	---	0	0	0
További ismeretterjesztő művek	---	0	0	0
Közérdekű vagy nem besorolt művek6	0	---	0	0
További közlemények7	1		0	0
Egyéb szerzőség8	0	---	0	0
Idézők szerkesztett művekre	---	---	0	0
Idézők disszertációban, egyéb típusban	---	---	66	71
Összes közlemény és összes idézőik	111	---	884	1069

Megjegyzések
A táblázat számai hivatkozások is. A számra kattintva a program listázza azokat a műveket, amelyeket a cellában összeszámlált.
--- : Nem kitölthető cella
[1] A hivatkozások a disszertáció és egyéb típusú idézők nélkül számolva. A disszertáció és egyéb típusú idézők összesítve a táblázat végén találhatók.
[2] Szerkesztőként nem részesedik a könyv idézéséből
[3] Csak a tudományos jellegű absztraktok.
[4] Minden további még el nem számolt tudományos mű (kivéve alkotás vagy oltalmi forma), ahol a szerző: szerző, szerkesztő, kritikai vagy forráskiadás készítője szerzőségű.
[5] A disszertációk és egyéb típusú idézők nélkül számolva. A sor értéke az "Összes tudományos közlemény" sor idézettségi adatait veszi alapul.
[6] Minden Közérdekű, Nem besorolt jellegű közlemény, ahol a szerző nem egyéb szerzőségű szerző.
[7] Ide értve minden olyan művet, mely a táblázat más, nevesített soraiban nem került összeszámlálásra.
[8] Minden olyan egyéb szerzőségű mű, ahol a szerző nem: szerző, szerkesztő, kritikai vagy forráskiadás készítője szerzőségű.

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Kvell Krisztián (Immunológia, biotechnológia)

Az MTMT által csatolt publikációs lista idézők számával

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Független idéző: 48 Függő idéző: 9 Összesen: 57

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Független idéző: 26 Függő idéző: 4 Összesen: 30

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Független idéző: 32 Függő idéző: 6 Összesen: 38

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Független idéző: 9 Függő idéző: 9 Összesen: 18

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Független idéző: 1 Függő idéző: 1 Összesen: 2

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Független idéző: 8 Függő idéző: 1 Összesen: 9

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Független idéző: 1 Összesen: 1

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Efficient transduction of primary human B lymphocytes and nondividing myeloma B cells with HIV-1–derived lentiviral vectors

Fabrice Bovia, Patrick Salmon, Thomas Matthes, Krisztian Kvell, Tuan H. Nguyen, Christiane Werner-Favre, Marc Barnet, Monika Nagy, Florence Leuba, Jean-François Arrighi, Vincent Piguet, Didier Trono, and Rudolf H. Zubler

We studied the transduction of primary human B lymphocytes and myeloma cells with lentiviral vectors. In peripheral blood B cells that had been activated with helper T cells (murine thymoma EL-4 B5) and cytokines, multiply attenuated HIV-1–derived vectors pseudotyped with vesicular stomatitis virus (VSV) G-envelope protein achieved the expression of green fluorescence protein (GFP) in 27% ± 12% (mean ± 1 SD; median, 27%) of B cells in different experiments. When compared in parallel cultures, the transducibility of B cells from different donors exhibited little variation. The human cytomegalovirus (CMV) promoter gave 4- to 6-fold higher GFP expression than did the human elongation factor-1α promoter. A murine retroviral vector pseudotyped with VSV G protein proved inefficient even in mitotically active primary B cells. B cells freshly stimulated with Epstein-Barr virus were also transducible by HIV vectors (24% ± 9%), but B cells activated with CD40 ligand and cytokines resisted transduction. Thus, different culture systems gave different results. Freshly isolated, nondividing myeloma cells were efficiently transduced by HIV vectors; for 6 myelomas the range was 14% to 77% (median, 28%) GFP$^+$ cells. HIV vectors with a mutant integrase led to no significant GFP signal in primary B or myeloma cells, suggesting that vector integration was required for high transduction. In conclusion, HIV vectors are promising tools for studies of gene functions in primary human B cells and myeloma cells for the purposes of research and the development of gene therapies. (Blood. 2003;101: 1727-1733)

Introduction

Efficient delivery of genes into primary human B lymphocytes would allow the investigation of gene functions in these cells for the purposes of research and the development of gene therapies. One could then test in mature B cells the promoters/genes potentially suitable for stem cell–based therapies for immunodeficiencies.[1] Vectors achieving the efficient transfection of primary B cells would most likely also be suitable for the delivery of genes into freshly collected B tumor cells—for example, for the development of immune-based anti–B-tumor therapies.[2] Various viral vectors are currently being studied for their ability to transduce hematopoietic cells.[3-5]

Retroviral vectors derived from murine leukemia virus (MLV)[6,7] can transfer genes into immortal human B-cell lines, such as lymphoblastoid cells,[8] and primary B precursors,[9] but they are inefficient for mature human B cells.[10,11] These simple retroviruses can transduce genes only into actively dividing cells,[12] but a potent T-independent mitogen for human B cells in vitro, such as lipopolysaccharide (LPS) for murine B cells, has not been found.[13] In addition, MLV vectors might not be well adapted for human B cells because of the host species difference. HIV-1 and HIV-derived pseudotyped lentiviral vectors efficiently integrate into human cells, irrespective of cell division.[14-22] High transgene expression from such vectors in human T cells or total lymphocytes has been reported.[23-25] Generally, productive HIV infection or lentivector-mediated transduction of truly quiescent lymphocytes has not been observed; activation, at least from G_0 to G_1, seems to be required.[23,25-28] Efficient transduction of primary acute lymphoblastic leukemia cells with a bicistronic HIV vector, leading to the expression of a cytokine (granulocyte macrophage–colony-stimulating factor [GM-CSF]) and an immunostimulatory molecule (CD80), has also been achieved,[29] indicating a potential use of such vectors in novel anti–B-tumor therapies.

In this study we investigated the transduction of peripheral blood B cells with multiply attenuated HIV vectors pseudotyped with vesicular stomatitis virus (VSV) G glycoprotein.[21] Efficient transduction of such B cells occurred after their activation in a culture system using murine EL-4 B5 thymoma cells as helper T cells in conjunction with human cytokines.[30-33] This system leads to proliferation and subsequent plasmocytic differentiation of all naive and memory human B subsets.[33] Nondividing, freshly isolated multiple myeloma cells were also efficiently transduced by HIV vector. By contrast, an MLV vector pseudotyped with VSV G protein was inefficient even in dividing B cells.

From the Division of Hematology, Department of Medicine, Department of Genetics and Microbiology, and Department of Dermatology, University Hospital, Geneva, Switzerland.

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F.B. and P.S. contributed equally to this work.

D.T. has declared a financial interest as consultant to Cell Genesis, a company whose potential product is related to the HIV-1 vectors used in this study.

Reprints: R. Zubler, Division of Hematology, University Hospital, 1211 Geneva-14, Switzerland; e-mail: rudolf.zubler@hcuge.ch.

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ARTICLE

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Transduction of CpG DNA-Stimulated Primary Human B Cells with Bicistronic Lentivectors

Krisztian Kvell,[1] Tuan H. Nguyen,[2] Patrick Salmon,[2] Frédéric Glauser,[1] Christiane Werner-Favre,[1] Marc Barnet,[1] Pascal Schneider,[3] Didier Trono,[2] and Rudolf H. Zubler[1,*]

[1]*Division of Hematology, Department of Internal Medicine, and* [2]*Department of Genetics and Microbiology, University Hospitals, 1211 Geneva-14, Switzerland*

[3]*Department of Biochemistry, University of Lausanne, 1066 Epalinges, Switzerland*

**To whom correspondence and reprint requests should be addressed. Fax: 41 22 372 72 88. E-mail: rudolf.zubler@hcuge.ch.*

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Recently, using HIV-1-derived lentivectors, we obtained efficient transduction of primary human B lymphocytes cocultured with murine EL-4 B5 thymoma cells, but not of isolated B cells activated by CD40 ligation. Coculture with a cell line is problematic for gene therapy applications or study of gene functions. We have now found that transduction of B cells in a system using CpG DNA was comparable to that in the EL-4 B5 system. A monocistronic vector with a CMV promoter gave 32 ± 4.7% green fluorescent protein (GFP)$^+$ cells. A bicistronic vector, encoding IL-4 and GFP in the first and second cistrons, respectively, gave 14.2 ± 2.1% GFP$^+$ cells and IL-4 secretion of 1.3 ± 0.2 ng/10^5 B cells/24 h. This was similar to results obtained in CD34$^+$ cells using the elongation factor-1α promoter. Activated memory and naive B cells were transducible. After transduction with a bicistronic vector encoding a viral FLIP molecule, vFLIP was detectable by FACS or Western blot in GFP$^+$, but not in GFP$^-$, B cells, and 57% of sorted GFP$^+$ B cells were protected against Fas ligand-induced cell death. This system should be useful for gene function research in primary B cells and development of gene therapies.

Key Words: HIV-1-derived lentivectors, bicistronic vectors, human primary B lymphocytes, CpG DNA, viral FLIP

INTRODUCTION

Optimization of methods for gene delivery into primary human cells is important for research on gene functions and development of gene therapies [1]. Gene transfer into primary human B lymphocytes has been notoriously difficult. Successful applications of nonviral methods to functional assays of transgenes have not been reported for these cells. Epstein–Barr virus vectors so far have been tested only in B cell lines [2]. Murine oncoretroviral vectors gave low transduction efficiency (of up to about 4%) in primary human B cells; they could be utilized to study effects detectable by very sensitive methods, such as immunoglobulin (Ig) class-switch recombination detectable by PCR [3]. HIV-1-derived lentivectors gave efficient transduction of various immature and mature human hematopoietic cells [4–6]. Transgene expression restricted to B lymphocytes was obtained by grafting lentivector-transduced CD34$^+$ progenitors into NOD/SCID mice [7]. T lymphocytes could be transduced after activation, at least from the G0 to the G1 stage of the cell cycle [5,6]. But primary human B cells activated into proliferation by crosslinking of CD40 in the presence of various cytokines were very poorly transducible [8,9]. Recently with such vectors we obtained efficient transduction of primary B cells cocultured with irradiated murine EL-4 B5 thymoma cells; monocistronic vectors with the human cytomegalovirus (CMV) or elongation factor-1α (EF-1α) internal promoter gave 27 ± 12% green fluorescent protein (GFP)$^+$ cells [9].

For gene therapy applications, however, a cell line potentially adds risks, such as generation of recombinant viruses. For studies of gene functions a handicap is that the functions of the thymoma cells have not yet been molecularly characterized. The first aim of this study was to find a culture system for transduction with HIV vectors of isolated B cells activated by defined stimuli. The LPS receptor, Toll-like receptor-4 (TLR4), is lacking in human B cells. But TLR9, the endosomal receptor for bacterial DNA (short single-stranded DNA containing nonmethylated CpG motifs; CpG DNA), is constitutively expressed in memory human B cells and rapidly upregulated by anti-Ig antibody—which mimics an antigen signal—in

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Species-specific restriction of cell surface expression of mouse MARCO glycoprotein in murine cell lines ☆

Krisztián Kvell [a], Tamás Czömpöly [a], Timo Pikkarainen [b], Péter Balogh [a,*]

[a] Department of Immunology and Biotechnology, Faculty of Medicine, University of Pécs, Szigeti út 12, H-7634 Pécs, Hungary
[b] Division of Matrix Biology, Department of Medical Biochemistry and Biophysics, Karolinska Institute, S-171 77 Stockholm, Sweden

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Abstract

The MARCO (macrophage receptor with collagenous structure) glycoprotein belongs to the scavenger receptor type family of pattern-recognition molecules produced by a subset of marginal zone macrophages in the spleen. Stimulation with LPS leads to its appearance on macrophages located at other tissue compartments. In the present work, we report its in vitro expression by various cell lines using transient and stable (lentiviral) gene delivery aimed at investigating the signaling properties of this receptor and its analysis using a novel rat monoclonal antibody against the SRCR-domain of mouse MARCO. When trying to establish stable mouse MARCO-transfectants using lentiviral transduction and other methods, we consistently found that MARCO accumulated intracellularly in various murine host cells. In contrast, such a phenomenon was not observed in non-murine cell lines. Our observations indicate the presence of an unexpected limitation of the in vitro expression of mouse MARCO glycoprotein in murine cell lines. We believe that the failure to express MARCO on the cell surface of the many murine cell lines is likely due to the absence of endoplasmic reticulum molecular chaperones needed for the correct folding and assembly of the trimeric MARCO molecule.

Keywords: Mouse MARCO; Lentiviral expression; Transgenic cell lines; IBL-12 mAb

The ability of the adaptive immune system to establish efficient immune responses requires the presence of organized lymphoid tissues, with a highly regulated distribution of its various stromal and hemopoietic cellular elements [1]. A substantial bulk of mobile leukocytes is continuously recirculating between various lymphoid organs, while the sessile stromal cells and a smaller fraction of hemopoietic cells remain stationed in their tissue environment. This latter group includes various macrophage cell types and a smaller subset of B cells comprising the marginal zone (MZ) of the spleen both in human and rodents [2]. These cells capture blood-borne pathogens, and launch T-independent immune responses, or to process these antigens towards the follicles for initiating T-dependent reactions. During this communication between various splenic compartments a considerable cellular re-distribution of MZ macrophages and B cells has been demonstrated to take place, regulated by various soluble factors, including chemokines and other compounds [3].

Scavenger receptors (SRs) constitute a diverse family of cell surface molecules, comprising eight different groups of transmembrane glycoproteins [4]. These membrane receptors expressed primarily by macrophages and endothelial subsets in the lymphoreticular tissues and elsewhere recognize a broad range of foreign polyanionic ligands, such as

☆ *Abbreviations:* AcLDL, acetylated low-density lipoprotein; AP, alkaline phosphatase; BSA, bovine serum albumin; cPPT sequence, central polypurine tract; FITC, fluorescein-isothiocyanate; GFP, green fluorescent protein; HRP, horseradish peroxidase; LPS, lipopolysaccharide; LTR, long terminal repeat; MAdCAM-1, mucosal addressin cell adhesion molecule-1; MARCO, macrophage receptor with collagenous structure; PBS, phosphate-buffered saline; NBT/BCIP, nitro-blue tetrazolium/bromchloro-indolyl-phosphate; SIN, self-inactivating long terminal repeat; SRCR, scavenger receptor cysteine-rich domain; TU, transforming unit; WPRE, woodchuck hepatitis virus post-transcriptional responsive element.

* Corresponding author.
E-mail address: peter.balogh@aok.pte.hu (P. Balogh).

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Review Article

Blurring Borders: Innate Immunity with Adaptive Features

K. Kvell,[1] EL. Cooper,[2] P. Engelmann,[1] J. Bovari,[1] and P. Nemeth[1]

[1] *Department of Immunology and Biotechnology, Faculty of Medicine, University of Pécs, 7624 Pécs, Hungary*
[2] *Laboratory of Comparative Neuroimmunology, Department of Neurobiology, David Geffen School of Medicine at UCLA, University of California, Los Angeles, CA 90095-1763, USA*

Correspondence should be addressed to P. Nemeth, peter.nemeth@aok.pte.hu

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Adaptive immunity has often been considered the penultimate of immune capacities. That system is now being deconstructed to encompass less stringent rules that govern its initiation, actual effector activity, and ambivalent results. Expanding the repertoire of innate immunity found in all invertebrates has greatly facilitated the relaxation of convictions concerning what actually constitutes innate and adaptive immunity. Two animal models, incidentally not on the line of chordate evolution (*C. elegans* and *Drosophila*), have contributed enormously to defining homology. The characteristics of specificity and memory and whether the antigen is pathogenic or nonpathogenic reveal considerable information on homology, thus deconstructing the more fundamentalist view. Senescence, cancer, and immunosuppression often associated with mammals that possess both innate and adaptive immunity also exist in invertebrates that only possess innate immunity. Strict definitions become blurred casting skepticism on the utility of creating rigid definitions of what innate and adaptive immunity are without considering overlaps.

1. INTRODUCTION: WHERE INNATE AND ADAPTIVE IMMUNITY CONVERGE

All multicellular animals (invertebrates and vertebrates) manage to keep self-integrity. Any attempt to answer questions concerning immune recognition must consider the universality of receptor-mediated responses. These may designate two forms: (1) rearranging clonally distributed antigen-specific receptors that distinguish between self and nonself according to classical Burnet hypothesis; and/or (2) pattern recognition receptors introduced by Janeway [1, 2]. The ideal immune system provides rapid and efficient responses, diverse repertoire of recognition, and effector molecules as well as specific memory on an individual level. In the self and nonself discrimination theory, the recognition receptors are central to immunity. However, a recently advanced hypothesis emphasizes that alarm signals have priority and initiate immune responses. These alarm danger signals released from the body's own cells are explained by the danger model of immunity. According to this model, immune cells must "decide" what poses harm to the body among self and nonself structures [3, 4]. The two branches of vertebrate immunity (innate and adaptive) are dependent on each other. The innate immune system, responsible for the first encounter with a pathogen, can trigger adaptive immunity in case the initial response is ineffective. Both arms interact with each other, via cell-cell interactions and soluble factors maintaining a physiological steady state [5].

With this in mind, we felt compelled to clarify and extend what seems to be the blurring or masking of certain immunological characteristics of invertebrates and vertebrates [6–8]. To do this, we first define the general features of innate and adaptive immunities. Innate immunity is considered to be natural, nonspecific, nonanticipatory, and nonclonal but germ-line encoded; whereas adaptive immunity is indeed specific, anticipatory, clonal, and somatic. Then, we discuss the blurring of vertebrate and invertebrate immunological characteristics in the following sections: (1) a preface to adaptive immunity; (2) senescence, cancer, and immunosuppressive viruses; (3) invertebrate immunological memory triggered by nonpathogenic stimuli; (4) the dawn of adaptive immunity; and (5) perspectives on innate and adaptive immunity.

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BASIC RESEARCH

Increased Chondrocyte Death after Steroid and Local Anesthetic Combination

Boglárka Farkas MD, Krisztián Kvell MD, PhD, Tamás Czömpöly MD, PhD, Tamás Illés MD, PhD, Tamás Bárdos MD, PhD

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Abstract

Background Hyaline articular cartilage has limited repair and regeneration capacity. Intraarticular administration of glucocorticoid and local anesthetic injections play an important role in the therapy of osteoarthritis. Glucocorticoids and anesthetics reportedly enhance apoptosis in chondrocytes, but effects of the combined use of glucocorticoids and local anesthetics are unknown.

Questions/purposes We asked whether glucocorticoid and local anesthetic agents combined had any synergistic effects on chondrocyte apoptosis.

Methods Cell viability and apoptosis/necrosis assessment of human articular chondrocytes were performed in vitro (chondrocyte cell cultures) and ex vivo (osteochondral specimens) using flow cytometry and TUNEL analysis, respectively.

Results Glucocorticoids and local anesthetics induce apoptosis in chondrocytes at various rates. When used in combination, the percentage of dead chondrocytes was increased in in vitro chondrocyte cell cultures and osteochondral ex vivo specimens.

Conclusions We observed a time-dependent decrease in chondrocyte viability after concurrent steroid and local anesthetic exposure.

Clinical Relevance The combination of glucocorticoids and local anesthetics has an adverse effect on articular chondrocytes, and it raises a question regarding whether concomitant administration should be used in treating osteoarthritis.

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B. Farkas, T. Illés, T. Bárdos (✉)
Department of Orthopaedics, University of Pécs, Ifjúság u. 13, 7624 Pécs, Hungary
e-mail: tbardos@hotmail.com

B. Farkas
Department of Anatomy, University of Pécs, Pécs, Hungary
e-mail: boglarka_farkas@hotmail.com

K. Kvell, T. Czömpöly
Department of Immunology and Biotechnology, University of Pécs, Pécs, Hungary

Introduction

Osteoarthritis is the most common form of joint disease and represents the most notable basis of disability afflicting greater than 5% of the world's population [11, 29]. Osteoarthritis is characterized by progressive erosion, degradation, and degeneration of the articular cartilage, osteophyte formation, and subchondral changes. If articular cartilage damage is not extensive, nonoperative treatment is preferable.

According to the European League Against Rheumatism (EULAR) recommendation, the optimal treatment of osteoarthritis constitutes a combination of nonpharmacologic and pharmacologic therapeutic modalities [1, 19, 22]. The nonoperative pharmacologic treatments include putative oral chondroprotective drugs (dietary supplements), oral or topical nonsteroidal antiinflammatory drugs, and intraarticular injections such as corticosteroids, local anesthetics, or viscosupplementing agents.

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PLoS one

Wnt4 and LAP2alpha as Pacemakers of Thymic Epithelial Senescence

Krisztian Kvell[1], Zoltan Varecza[1], Domokos Bartis[1], Sebastian Hesse[1], Sonia Parnell[2], Graham Anderson[2], Eric J. Jenkinson[2], Judit E. Pongracz[1,2]*

1 Department of Medical Biotechnology, Institute for Immunology and Biotechnology, University of Pecs, Pecs, Hungary, **2** Division of Immunity and Infection, Department of Anatomy, Institute for Biomedical Research, University of Birmingham, Birmingham, United Kingdom

Abstract

Age-associated thymic involution has considerable physiological impact by inhibiting *de novo* T-cell selection. This impaired T-cell production leads to weakened immune responses. Yet the molecular mechanisms of thymic stromal adipose involution are not clear. Age-related alterations also occur in the murine thymus providing an excellent model system. In the present work structural and molecular changes of the murine thymic stroma were investigated during aging. We show that thymic epithelial senescence correlates with significant destruction of epithelial network followed by adipose involution. We also show in purified thymic epithelial cells the age-related down-regulation of Wnt4 (and subsequently FoxN1), and the prominent increase in LAP2α expression. These senescence-related changes of gene expression are strikingly similar to those observed during mesenchymal to pre-adipocyte differentiation of fibroblast cells suggesting similar molecular background in epithelial cells. For molecular level proof-of-principle stable LAP2α and Wnt4-over-expressing thymic epithelial cell lines were established. LAP2α over-expression provoked a surge of PPARγ expression, a transcription factor expressed in pre-adipocytes. In contrast, additional Wnt4 decreased the mRNA level of ADRP, a target gene of PPARγ. Murine embryonic thymic lobes have also been transfected with LAP2α- or Wnt4-encoding lentiviral vectors. As expected LAP2α over-expression increased, while additional Wnt4 secretion suppressed PPARγ expression. Based on these pioneer experiments we propose that decreased Wnt activity and increased LAP2α expression provide the molecular basis during thymic senescence. We suggest that these molecular changes trigger thymic epithelial senescence accompanied by adipose involution. This process may either occur directly where epithelium can trans-differentiate into pre-adipocytes; or indirectly where first epithelial to mesenchymal transition (EMT) occurs followed by subsequent pre-adipocyte differentiation. The latter version fits better with literature data and is supported by the observed histological and molecular level changes.

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* E-mail: judit.e.pongracz@aok.pte.hu

Introduction

Thymic senescence

Thymic senescence begins early, around late puberty. This process is called adipose involution, as the thymus is invaded by adipose tissue [1]. Due to decrease in thymic epithelial tissue mass, the thymus can no longer support the same output of T-cell production [2]. Therefore peripheral blood T lymphocyte composition exhibits the dominance of memory T lymphocytes resulting in impaired responses towards novel, particularly viral infections [3,4,5]. Since the thymic epithelium has a key role in deleting auto-reactive T-cell clones, functional impairment increases the chances of developing auto-immune disease [6]. If we were able to slow down or even stop the loss of thymic epithelium the elderly would have a better chance to address late-onset autoimmune diseases and viral infections. However, despite studies of thymic senescence, the molecular mechanism of thymic aging remains elusive.

Signaling pathways of thymic epithelial cell development and maintenance

Understanding signaling mechanisms that regulate tissue development and maintenance of thymic epithelial cells might reveal the process of adipose involution. Certainly, maintenance and functional integrity of the thymic stroma requires stimuli through Notch, BMP, and Wnt signaling pathways [7,8,9,10,11]. Undoubtedly, the Wnt family of secreted glycoproteins is one of the best analyzed among the required ligands [12]. Most members of the nineteen known Wnt glycoproteins have been implicated in both the development of embryonic thymus and the maintenance of adult thymic epithelium [13]. In the thymus, Wnt ligands originate primarily from thymic epithelial cells and activate a highly complex signaling network via ten G-protein dependent receptors called Frizzleds (Fz), and their co-receptors of low-density lipoprotein receptor-related proteins 5/6 called LRP5/6 [14,15]. The actual constellation of ligands, receptors, co-receptors and further regulatory molecules define Wnt-mediated effects.

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BRIEF COMMUNICATION

Characterisation of eGFP-transgenic BALB/c mouse strain established by lentiviral transgenesis

Krisztián Kvell · Tamás Czömpöly · László Hiripi · Péter Balogh · József Kóbor · Lilla Bodrogi · Judit E. Pongrácz · William A. Ritchie · Zsuzsanna Bősze

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Abstract Lentiviral technology is a powerful tool for the creation of stable transgenic animals. However, uncertainties have remained whether constitutive promoters resist long-term silencing. We used concentrated HIV-1 based lentiviral vectors to create stable transgenic BALB/c mice by perivitelline injection. In our vectors eGFP expression was driven by the human EF1α promoter. The established transgenic animals were analyzed for eGFP expression by in vivo fluorescence imaging, PCR, histology and flow-cytometry. eGFP expression showed even distribution without mosaicism; however, tissue-dependent differences of eGFP expression were observed. Up to the sixth generation only one newborn showed eGFP inactivation. eGFP + transgenic bone marrow cells efficiently provided long-term haemopoietic repopulation in radiation chimeras, regenerating all bone marrow-derived lineages with eGFP + cells with distinct eGFP expression profiles. The established eGFP + BALB/c mouse strain is expected to be extremely useful in various immunological experiments.

Keywords Balb/c · eGFP · Lentiviral transgenesis · Bone-marrow chimeric mouse

K. Kvell · T. Czömpöly · P. Balogh · J. E. Pongrácz
Department of Immunology and Biotechnology, University of Pecs, Pecs, Hungary

L. Hiripi · L. Bodrogi · Z. Bősze (✉)
Genetic Modification Program Group, Agricultural Biotechnology Center, P. O. Box 411, 2100 Gödöllő, Hungary
e-mail: bosze@abc.hu

J. Kóbor
Department of Oncotherapy, University of Pecs, Pecs, Hungary

W. A. Ritchie
Roslin Embryology Limited, Edinburgh, Scotland, UK

Introduction

Lentiviral transgenesis has become an important and efficient new tool for the establishment of transgenic animals. The transgenic sequence most often used for 'proof-of-principle'-type experiments is eGFP (enhanced green fluorescent protein). Concentrated lentiviral vectors efficiently transfect zygotes following perivitelline injection. With this method the nucleus of the zygote is not affected directly, and higher volumes may be injected with less sophisticated machinery. With lentiviral vectors the efficiency of stable, active transgenesis is significantly higher than with standard pronuclear injection, reaching 8–50% (Park 2007).

In the field of immunology a massive body of experimental evidence is derived from studies performed in mice with BALB/c genetic background (Bleul et al. 2006; Ivanov et al. 2006; Odegaard et al.

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Multiple suppression pathways of canonical Wnt signalling control thymic epithelial senescence

Zoltan Varecza [a], Krisztian Kvell [a], Gergely Talabér [a], Gyorgy Miskei [a], Veronika Csongei [a], Domokos Bartis [a], Graham Anderson [b], Eric J. Jenkinson [b], Judit E. Pongracz [a,*]

[a] Department of Medical Biotechnology, Institute for Immunology and Biotechnology, Faculty of Medicine, University of Pécs, Pécs, Hungary
[b] Institute for Biomedical Research, Faculty of Medicine, University of Birmingham, Birmingham, UK

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ABSTRACT

Members of the Wnt family of secreted glyco-lipo-proteins affect intrathymic T-cell development and are abundantly secreted by thymic epithelial cells (TECs) that create the specific microenvironment for thymocytes to develop into mature T-cells. During ageing, Wnt expression declines allowing adipoid involution of the thymic epithelium leading to reduced naïve T-cell output. The protein kinase C (PKC) family of serine-threonine kinases is involved in numerous intracellular biochemical processes, including Wnt signal transduction. In the present study, PKCδ expression is shown to increase with age and to co-localise with Wnt receptors Frizzled (Fz)-4 and -6. It is also demonstrated that connective tissue growth factor (CTGF) is a Wnt-4 target gene and is potentially involved in a negative feed-back loop of Wnt signal regulation. Down-regulation of Wnt-4 expression and activation of multiple repressor pathways suppressing β-catenin dependent signalling in TECs contribute to the initiation of thymic senescence.

1. Introduction

During ageing of the immune system the gradual loss of naïve T-cells is associated with the rate of thymic adipose involution that correlates with significant destruction of the epithelial network. As impaired T-cell production leads to weakened immune responses, understanding the mechanism of thymic involution has high physiological and medical importance.

In our recent studies of thymic involution Wnt-4 secretion was significantly reduced in TECs while LAP2α expression concomitantly increased triggering epithelial–mesenchymal transition (EMT) and then pre-adipocyte-differentiation (Kvell et al., 2010).

As Wnt-4 is the primary regulator of FoxN1 expression and consequently TEC identity, understanding Wnt-4 signalling carries particularly high importance (Balciunaite et al., 2002). The difficulty of signalling studies, however, stems from the general complexity of Wnt pathways (Kuhl and Pandur, 2009). Wnt-4, for example, has been described as activator of both β-catenin dependent canonical (Lyons et al., 2004) and JNK/PKC dependent non-canonical (Cai et al., 2002; Du et al., 1995) signalling pathways that interact at multiple levels. Apart from specific, there are also shared signalling elements in Wnt pathways including the main cell surface receptors Frizzleds (Fz) (Schulte and Bryja, 2007) as well as intracellular signalling molecules including G proteins (Malbon et al., 2001), Dishevelleds (Dvl) (Kuhl et al., 2001; Schulte and Bryja, 2007) and PKCs α (Kuhl et al., 2001), ζ (Ossipova et al., 2003), and δ (Kinoshita et al., 2003). PKCδ appears particularly important as this serine-threonin kinase can phosphorylate and therefore activate Dvls (Kinoshita et al., 2003) to relay ligand induced signals towards down-stream elements of Wnt cascades.

From the ten known mammalian Fz receptors, Fz-4 (Lyons et al., 2004) and Fz-6 (Lyons et al., 2004) have been confirmed to bind Wnt-4. Interestingly, while Fz-4 is an activator of the β-catenin dependent canonical pathway, signals from Fz-6 inhibit β-catenin dependent target gene transcription (Golan et al., 2004) indicating that regulation of Wnt-4 signalling might also begin at receptor level in the thymus.

As thymic involution is a complex physiological process and appears to be initiated by suppression of Wnt signals, understanding of receptor associated regulatory mechanisms can lead to target molecule recognition in the quest for re-juvenate the ageing thymus. To investigate the hypothesis, TECs of young and ageing adult Balb/c mice as well as a thymic epithelial cell line, TEP1 were used in the studies. Our experiments demonstrate that expression of Wnt receptors increase with age and that Frizzleds co-localize

* Corresponding author at: Department of Medical Biotechnology, Institute for Immunology and Biotechnology, Faculty of Medicine, University of Pécs, 12 Szigeti, Pécs H-7624, Hungary. Tel.: +36 72 536 288; fax: +36 72 536 289.
E-mail address: judit.e.pongracz@aok.pte.hu (J.E. Pongracz).

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Wnt-4 Protects Thymic Epithelial Cells against Dexamethasone-Induced Senescence

Gergely Talaber,[1] Krisztian Kvell,[1] Zoltan Varecza,[1] Ferenc Boldizsar,[1] Sonia M. Parnell,[2] Eric J. Jenkinson,[2] Graham Anderson,[2] Timea Berki,[1] and Judit E. Pongracz[1]

Abstract

Glucocorticoids are widely used immunosuppressive drugs in treatment of autoimmune diseases and hematological malignancies. Glucocorticoids are particularly effective immune suppressants, because they induce rapid peripheral T cell and thymocyte apoptosis resulting in impaired T cell–dependent immune responses. Although glucocorticoids can induce apoptotic cell death directly in developing thymocytes, how exogenous glucocorticoids affect the thymic epithelial network that provides the microenvironment for T cell development is still largely unknown. In the present work, we show that primary thymic epithelial cells (TECs) express glucocorticoid receptors and that high-dosage dexamethasone induces degeneration of the thymic epithelium within 24 h of treatment. Changes in organ morphology are accompanied by a decrease in the TEC transcription factor FoxN1 and its regulator Wnt-4 parallel with upregulation of lamina-associated polypeptide 2α and peroxisome proliferator activator receptor γ, two characteristic molecular markers for adipose thymic involution. Overexpression of Wnt-4, however, can prevent upregulation of adipose differentiation-related aging markers, suggesting an important role of Wnt-4 in thymic senescence.

Introduction

Autoimmune diseases and hematological malignancies are significant causes of morbidity and mortality world wide.[1,2] Although research is ongoing, treatment options are still often limited to high-dosage synthetic glucocorticoid (GC) analogs despite their nonspecificity and multiple side effects. Indeed, GCs are still applied in therapy for acute and chronic autoimmune diseases and hematological malignancies,[3,4] because they effectively promote apoptosis of leukemia cells[5] and trigger complex antiinflammatory actions by influencing both molecular and cellular components of the immune system.[6] Apart from triggering decreased expression of cytokines and major histocompatibility complex class II (MHC II), GCs also induce apoptotic death of peripheral[7] and developing T cells. In mouse models, GCs cause massive thymocyte depletion, especially in the $CD4^+CD8^+$ (double positive [DP]) thymocyte population,[8–12] blocking *de novo* T cell production.

Prior experiments have also demonstrated that high-dose GCs induce a dramatic[13] and apoptosis-associated[14] involution of the thymus, and not only thymocytes but also thymic epithelial cells (TECs) are seriously affected.[15] Additionally, a recent report by Fletcher et al.[16] has highlighted that TEC depletion appears reversible, and thymic epithelial stem cells play an important role in this process.

Because physiological steroids are implicated in the regulation of aging,[17,18] we theorized that GC treatment might affect thymic epithelial senescence. Although morphological similarities between physiological and induced thymic involution are striking, to date the process has not been studied in detail at the molecular level. One possible mechanism is that during physiological aging TECs undergo epithelial-to-mesenchymal transition (EMT) and then proadipose differentiation.[19,20] Our studies have recently provided evidence that this process is regulated by Wnt-4 and FoxN1 decline, leading to drastic reduction in TEC identity[21,22] and simultaneous upregulation of lamina-associated polypeptide (LAP) 2α as well as preadipocyte-related markers peroxisome proliferator activator receptor (PPAR) γ and adipose differentiation-related protein (ADRP).[20]

On the basis of the above studies, we theorized that GCs do not simply deplete thymocytes and the majority of TECs, but they also inhibit the function of the remaining epithelium via downregulation of characteristic TEC markers, leading to preadipocyte differentiation. In the present study, we provide evidence that both primary TECs and the primary TEC-derived TEP1 cell line express glucocorticoid receptors (GRs)

[1]Department of Immunology and Biotechnology, University of Pecs, Faculty of Medicine, Pecs, Hungary.
[2]Department of Anatomy, Institute for Biomedical Research, Faculty of Medicine, University of Birmingham, United Kingdom.

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Fine-tuning of proximal TCR signaling by ZAP-70 tyrosine residues in Jurkat cells

M. Szabo, T. Czompoly, K. Kvell, G. Talaber, D. Bartis, P. Nemeth, T. Berki and **F. Boldizsar**

Department of Immunology and Biotechnology, University of Pecs, H-7643 Pecs, Hungary

Correspondence to: F. Boldizsar, Department of Immunology and Biotechnology, University of Pecs, H-7643 Pecs, Szigeti ut 12, Hungary; E-mail: ferenc.boldizsar@aok.pte.hu

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Abstract

Zeta-chain-associated protein kinase of 70kDa (ZAP-70) kinase is a key regulator in the early steps of TCR signaling but some aspects of its fine regulation are still unclear. From its 31 tyrosine (Y) residues, 11 phosphorylation sites have been identified, some with activator (Y315 and Y493) or inhibitory (Y292 and Y492) and others with unknown function (Y069, Y126 and Y178). In our present work, we aimed to elucidate the role of different Y residues of ZAP-70, especially those with unknown function, in calcium signaling and the autoregulation of the kinase. ZAP-70-deficient Jurkat cells (P116) were stably reconstituted with point-mutated ZAP-70 constructs where tyrosine residues 069, 126, 178, 238, 292, 315, 492 or 493 were replaced with phenylalanine (F). The anti-CD3-elicited calcium signal increased in F069-, F292- and F492-ZAP-70-expressing cell lines but decreased in the F126-, F315- and F493-ZAP-70-expressing cell lines. ZAP-70 point mutations led to phosphorylation changes predominantly in SH2 domain containing leukocyte protein of 76kDa (SLP-76) but not linker of activated T cells (LAT) during CD3-activation; moreover, we detected basal hyperphosphorylation of SLP-76 Y128 in the F126-, F178- and F492-ZAP-70-expressing cell lines. In summary, Y069, Y178, Y292 and Y492 have inhibitory, while Y126, Y315 and Y493 activator role in anti-CD3-induced T-cell activation. Phosphorylation changes in LAT and SLP-76 suggest that fine regulation of ZAP-70 on calcium signaling is rather transmitted through SLP-76 not LAT. Additionally, negative or positive autoregulatory function of Y292 and Y493 or Y315, respectively, was revealed in ZAP-70. These data indicate that previously not characterized Y069, Y126 and Y178 in ZAP-70 participate in the fine regulation of TCR signaling.

Keywords: lentiviral transfection, site-directed mutagenesis, TCR signaling, ZAP-70

Introduction

T cells are key players of adaptive immunity: they recognize peptide antigens with their TCR in an MHC-restricted manner (1, 2), which leads to their activation/differentiation and the engagement of effector mechanisms. Co-receptors, like CD4 or CD8, CD28 and the protein tyrosine phosphatase CD45 are also involved in TCR-mediated signaling (3–5). A complex network of signaling events is prerequisite for T-cell activation. Upon close TCR–peptide–MHC binding, early phosphorylation steps are initiated. First, the sarcoma (Src) non-receptor tyrosine kinase family member, lymphocyte-specific protein tyrosine kinase (Lck) (CD4/8 associated) is primed by the phosphatase CD45 through the removal of an inhibitory phosphate group from tyrosine (Y)505 (6). Next, Lck is activated by the phosphorylation of Y394 by the activated TCR complex (6). The activated Lck, in turn, phosphorylates immunoreceptor tyrosine-based activation motifs found in the TCR-associated CD3 complex (7). The phosphorylated CD3 ζ chain provides a docking site for the spleen tyrosine kinase (Syk) family member zeta-chain-associated protein kinase of 70kDa (ZAP-70) kinase (8).

ZAP-70 is phosphorylated by Lck and activated to become a key organizer of downstream TCR signaling steps. Two important target molecules of the ZAP-70 are the adapter proteins linker of activated T cells (LAT) and SH2 domain containing leukocyte protein of 76kDa (SLP-76) (9–11). Phosphorylation of these molecules leads to the formation of a multimolecular complex involving growth factor receptor-bound protein 2 (GRB2), IL2-inducible T-cell kinase, GRB2-related adaptor downstream of Src homology 2 domain containing transforming protein (Shc) and Vav that results in activation of phospholipase C-γ1 (PLCγ1) (12, 13). PLCγ1, in turn, cleaves phosphatidylinositol 4,5-bisphosphate producing two second messengers: inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG) (14). DAG initiates two major pathways

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PLOS ONE

Down-Regulation of Canonical and Up-Regulation of Non-Canonical Wnt Signalling in the Carcinogenic Process of Squamous Cell Lung Carcinoma

Domokos Bartis[1,2☯], Veronika Csongei[1,6☯], Alexander Weich[1], Edit Kiss[1,6], Szilvia Barko[3], Tamas Kovacs[1,6], Monika Avdicevic[1], Vijay K. D'Souza[2], Judit Rapp[1,6], Krisztian Kvell[1,6], Laszlo Jakab[4], Miklos Nyitrai[2,6], Tamas F. Molnar[4], David R. Thickett[2], Terezia Laszlo[5], Judit E. Pongracz[1,6]*

1 Department of Medical Biotechnology, Institute of Immunology and Biotechnology, Medical School, University of Pecs, Pecs, Hungary, **2** Department of Medicine, Medical School, University of Birmingham, Birmingham, United Kingdom, **3** Department of Biophysics, Medical School, University of Pecs, Pecs, Hungary, **4** Department of Surgery, Medical School, University of Pecs, Pecs, Hungary, **5** Department of Pathology, Medical School, University of Pecs, Pecs, Hungary, **6** Szentagothai Research Center, University of Pecs, Pecs, Hungary

Abstract

The majority of lung cancers (LC) belong to the non-small cell lung carcinoma (NSCLC) type. The two main NSCLC sub-types, namely adenocarcinoma (AC) and squamous cell carcinoma (SCC), respond differently to therapy. Whereas the link between cigarette smoke and lung cancer risk is well established, the relevance of non-canonical Wnt pathway up-regulation detected in SCC remains poorly understood. The present study was undertaken to investigate further the molecular events in canonical and non-canonical Wnt signalling during SCC development. A total of 20 SCC and AC samples with matched non-cancerous controls were obtained after surgery. TaqMan array analysis confirmed up-regulation of non-canonical Wnt5a and Wnt11 and identified down-regulation of canonical Wnt signalling in SCC samples. The molecular changes were tested in primary small airway epithelial cells (SAEC) and various lung cancer cell lines (e.g. A549, H157, etc). Our studies identified Wnt11 and Wnt5a as regulators of cadherin expression and potentiated relocation of β-catenin to the nucleus as an important step in decreased cellular adhesion. The presented data identifies additional details in the regulation of SCC that can aid identification of therapeutic drug targets in the future.

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* E-mail: judit.e.pongracz@aok.pte.hu

☯ These authors contributed equally to this work.

Introduction

Lung cancer (LC) is the leading cause of cancer death worldwide [1]. About 80% of LCs belongs to the NSCLC type which is erroneously considered as a single entity. The two main NSCLC sub-types, namely AC that arises mostly in the peripheral airways or the bronchio-alveolar region of the parenchyma, and SCC that develops mainly in the proximal airways and affects mostly cigarette smokers, differs not only in aggressiveness but responsiveness to chemotherapy, also. To make the overall picture more complicated, there are an emerging number of combined NSCLCs where malignant tumours are representing themselves as adeno-squamous or mixed type LC. Not surprisingly, the molecular background of AC and SCC development has been a focus of intense investigation. In various studies Wnt signalling has emerged as one of the potential regulators of the carcinogenic process.

Wnt Signalling

Wnt signalling regulates a variety of developmental processes including cell fate specification, proliferation, polarity and migration (reviewed in [2]). Wnt molecules trigger gene transcription via at least three signalling pathways: the canonical or β-atenin dependent, and two non-canonical pathways. When Wnts bind to their trans-membrane receptors, Frizzleds (Fzd) and co-receptors, LRP5/6, signal transduction begins on the canonical pathway. Once stabilized, non-degraded β-catenin molecules move to the nucleus where they activate TCF-LEF-dependent gene transcription. In the absence of Wnt signals, the cytoplasmic β-catenin is subjected to phosphorylation in the APC-Axin-GSK3β-complex [2] then to subsequent proteasomal degradation. Upon non-canonical Wnt signals, the JNK/AP1 dependent, planar cell polarity (PCP) and the PKC/CAMKII/NFAT dependent Ca^{2+} pathways are activated.

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Alteration in the Wnt microenvironment directly regulates molecular events leading to pulmonary senescence

Tamas Kovacs,[1,2] Veronika Csongei,[1,2] Diana Feller,[1,2] David Ernszt,[1,2] Gabor Smuk,[3] Veronika Sarosi,[4] Laszlo Jakab,[5] Krisztian Kvell,[1,2] Domokos Bartis[6] and Judit E. Pongracz[1,2]

[1]Medical School, Department of Pharmaceutical Biotechnology, University of Pécs, Pécs, Hungary
[2]János Szentágothai Research Centre, University of Pécs, Pécs, Hungary
[3]Medical School, Department of Pathology, University of Pécs, Pécs, Hungary
[4]Medical School, Department of Pulmonology, University of Pécs, Pécs, Hungary
[5]Medical School, Department of Surgery, University of Pécs, Pécs, Hungary
[6]Department of Clinical Respiratory Sciences, Centre for Translational Inflammation Research, University of Birmingham Research Laboratories, Queen Elizabeth Hospital, Birmingham, UK

Summary

In the aging lung, the lung capacity decreases even in the absence of diseases. The progenitor cells of the distal lung, the alveolar type II cells (ATII), are essential for the repair of the gas-exchange surface. Surfactant protein production and survival of ATII cells are supported by lipofibroblasts that are peroxisome proliferator-activated receptor gamma (PPARγ)-dependent special cell type of the pulmonary tissue. PPARγ levels are directly regulated by Wnt molecules; therefore, changes in the Wnt microenvironment have close control over maintenance of the distal lung. The pulmonary aging process is associated with airspace enlargement, decrease in the distal epithelial cell compartment and infiltration of inflammatory cells. qRT–PCR analysis of purified epithelial and nonepithelial cells revealed that lipofibroblast differentiation marker parathyroid hormone-related protein receptor (PTHrPR) and PPARγ are reduced and that PPARγ reduction is regulated by Wnt4 via a β-catenin-dependent mechanism. Using a human *in vitro* 3D lung tissue model, a link was established between increased PPARγ and pro-surfactant protein C (pro-SPC) expression in pulmonary epithelial cells. In the senile lung, both Wnt4 and Wnt5a levels increase and both Wnt-s increase myofibroblast-like differentiation. Alteration of the Wnt microenvironment plays a significant role in pulmonary aging. Diminished lipo- and increased myofibroblast-like differentiation are directly regulated by specific Wnt-s, which process also controls surfactant production and pulmonary repair mechanisms.

Key words: molecular biology of aging; pulmonary senescence; Wnt microenvironment.

Correspondence
Dr. Judit E. Pongracz, Medical School, Department of Pharmaceutical Biotechnology, Szentágothai Research Centre, University of Pecs, 12 Szigeti Str, Pecs 7624, Hungary. Tel.: +36 30 435 7944; fax: +36 72 501 654; e-mail: pongracz.e.judit@pte.hu

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Introduction

In the aging lung, the total tissue mass decreases along with the number of capillaries. Formation of new alveoli is also limited. Due to decrease in tissue mass as well as muscle weakness, lung capacity declines with age even in healthy individuals (Tolep *et al.*, 1995; Polkey *et al.*, 1997). As senescence progresses, lung tissue becomes prone to inflammation, fibrosis and tumors demolishing lung capacity. Infections are frequent in the pulmonary tract of the elderly, leading to a chronic cycle of injury and repair that causes significant changes in the structure, function and gene expression of alveolar epithelial cells contributing to the development of chronic pulmonary diseases (Baarsma *et al.*, 2011; Chilosi *et al.*, 2012). Studies suggest that the senile lung is characterized by airspace enlargement similar to acquired emphysema (Verbeken *et al.*, 1992) even detected in nonsmokers above 50 years of age (Sharma & Goodwin, 2006; Calvi *et al.*, 2011). Similarly to humans, aging of the mouse lung is associated with homogeneous airspace enlargement.

The aging process of the lung is complex both in test animals and humans. Apart from decreased ability to withstand infections, low level chronic inflammatory processes are frequently detected (Meyer *et al.*, 1996). The low level chronic inflammation is associated with tissue destruction requiring effective tissue regeneration (Crosby & Waters, 2010) coordinated by epithelial progenitor cells. The progenitor cells originate from the five putative stem cell niches primarily identified in the lungs of mice (Engelhardt, 2001). The cells responsible for cellular regeneration in the bronchiolar region are the nonciliated epithelial cuboid Clara cells (Park *et al.*, 2006) while in the gas-exchange region of the alveoli, ATII cells drive the regenerative process. ATII cells are capable of transdifferentiation into ATI cells (Crosby & Waters, 2010; Rock *et al.*, 2011; Barkauskas *et al.*, 2013) providing the gas exchange surface of alveoli. ATII cells are also important in producing surfactant proteins responsible for lowering surface tension in the alveoli aiding gas exchange and stabilizing alveolar structure (Rooney *et al.*, 1994) Surfactants also have immune-modulatory activity in the host defense system (Veldhuizen & Possmayer, 2004; Maina *et al.*, 2010) making the presence of a well-maintained ATII cell population essential.

Although ATII cells are vitally important, ATII-s are unable to take up triglycerides directly from the blood and need the help of lipofibroblasts (Torday *et al.*, 1995; Rehan & Torday, 2012). Lipofibroblasts can take up triglycerides and accumulate lipid droplets generated by a proliferator-activated receptor gamma (PPARγ) (Ferguson *et al.*, 2009) and adipose differentiation-related protein (ADRP) (Gao & Serrero, 1999; Schultz *et al.*, 2002)-dependent mechanism.

In recent studies, the secreted Wnt glycolipoprotein ligand family (Pongracz & Stockley, 2006) have been reported to regulate both aging (Brack *et al.*, 2007) and PPARγ activity (Takada *et al.*, 2009; Talaber *et al.*, 2011). The two main and best characterized Wnt pathways are the β-catenin-dependent or canonical and the β-catenin-independent or noncanonical pathways (Pongracz & Stockley, 2006). While the canonical Wnts antagonize the PPARγ function (Takada *et al.*, 2009), noncanonical Wnts have not been reported to affect PPARγ transcription or activity. Recent studies conducted in aging mice have connected PPARγ to lipofibroblast differentiation (Willis & Borok, 2007; Paxson

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Active Wnt/beta-catenin signaling is required for embryonic thymic epithelial development and functionality *ex vivo*

Krisztian Kvell[a,*], Aniko V. Fejes[a], Sonia M. Parnell[b], Judit E. Pongracz[a,b]

[a] Department of Pharmacological Biotechnology, University of Pecs, Hungary
[b] Department of Anatomy, Division of Immunity and Infection, Institute for Biomedical Research, University of Birmingham, UK

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ABSTRACT

The Wnt/beta-catenin signaling pathway plays an important role in the commitment and development of thymic epithelial precursors. Here we document similarities of thymic epithelial development during embryogenesis in human and mouse. We stained for thymic epithelial surface markers (EpCAM1, Ly51, K8) and ligand/receptor pair (Wnt4, Fz4). Our results confirm the relevance of using murine test systems to model human embryonic thymic epithelial cell development.

We have efficiently transduced murine embryonic epithelial cells using mock (GFP) and Wnt/beta-catenin-inhibiting (ICAT-encoding) recombinant adenoviral vectors. The effect of Wnt4 was assayed in the form of Wnt4-containing supernatant. Gene expressional changes were assessed by Q-PCR and also morphology using conventional and confocal fluorescent microscopy. Functional aberration caused by ICAT was assessed through evaluation of thymocyte maturation.

Our results demonstrate that ICAT and Wnt4 have reciprocal effects during embryonic thymic epithelial cell development. While Wnt4 is capable of increasing the expression level of characteristic intracellular (FoxN1), surface (MHCII) and secreted (IL7) molecules, Wnt/beta-catenin inhibition through ICAT can moderately decrease their expression. Morphological changes induced by ICAT resulted in the development of hollow, inflated thymic lobes with reduced epithelial cell numbers. The ICAT-treated thymic lobes also showed significant impairment in supporting thymocyte development and maturation.

Introduction

Along with Notch and BMP, the abundantly secreted Wnt (wingless-related MMTV integration site) glycoproteins have been proposed to play an elementary role in the development, maintenance and functional integrity of the thymic stroma (Bleul and Boehm 2005; Pongracz et al. 2003; Osada et al. 2006; Anderson et al. 2001). The current article focuses on the evolutionarily conserved molecular family of secreted Wnt glycoproteins. The nineteen known Wnt glycoproteins signal through ten G-protein dependent receptors, called Frizzled receptors. For active signal transduction, Frizzled receptors need to form a complex with low density lipoprotein receptor-related proteins (LRP), as co-receptors. The actual constellation of the ligand, receptor and co-receptor defines Wnt-mediated effects in a context-dependent manner (Mikels and Nusse 2006; Gordon and Nusse 2006; Schweizer and Varmus 2003). Wnt4 is in spotlight of the current work being one of the most abundantly expressed non-canonical Wnt molecule secreted by the thymic epithelium during embryonic development, with expression levels progressively decreasing during postnatal development and aging (Kvell et al. 2010; Kvell and Pongracz 2011; Varecza et al. 2011). It is of note that FoxN1 (a key transcription factor that defines thymic epithelial identity) is an acknowledged target gene of Wnt4 in the thymic epithelial context (Balciunaite et al. 2002). ICAT (inhibitor of beta-catenin and TCF-4) is a polypeptide that inhibits Wnt/beta-catenin nuclear signaling by binding and competing its interaction with the transcription factor TCF (T cell factor) in the nucleus. Therefore ICAT is an intracellular negative regulator of the Wnt/beta-catenin pathway (Pongracz et al. 2006). Since the Wnt glycoproteins and Wnt4 in particular are key players of embryonic thymic epithelial development we examined the effect of both increased Wnt-effect (additional Wnt4 in the form of supernatant)

Abbreviations: BMP, bone morphogenic protein; EpCAM, epithelial cell adhesion molecule; FoxN1, forkhead box N1; Fz, frizzled; GFP, green fluorescent protein; ICAT, inhibitor of beta-catenin; IL7, interleukin 7; K, keratin; LRP, low density lipoprotein receptor-related proteins; MHCII, major histocompatibility complex II; TCF, T-cell factor; rAd, recombinant adeno-viruses; Wnt, wingless-related MMTV integration site.

* Corresponding author at: Department of Pharmacological Biotechnology, University of Pecs, 20 Ifjusag Street, H-7624 Pecs, Hungary. Tel.: +36 72 536 000/29250.
E-mail address: kvell.krisztian@pte.hu (K. Kvell).

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RESEARCH ARTICLE

Thymic Atrophy and Apoptosis of $CD4^+CD8^+$ Thymocytes in the Cuprizone Model of Multiple Sclerosis

Izabella Solti[1☯], Krisztian Kvell[2☯], Gergely Talaber[3], Sara Veto[1], Peter Acs[4], Ferenc Gallyas, Jr.[1,5,6], Zsolt Illes[7], Katalin Fekete[1], Petra Zalan[1], Arpad Szanto[8], Zita Bognar[1]*

1 Department of Biochemistry and Medical Chemistry, University of Pecs, Pecs, Hungary, **2** Department of Pharmaceutical Biotechnology, University of Pecs, Pecs, Hungary, **3** Karolinska Institutet, Department of Biosciences and Nutrition, NOVUM, Huddinge, Sweden, **4** Department of Neurology, University of Pecs, Pecs, Hungary, **5** MTA-PTE Nuclear-Mitochondrial Research Group, Pecs, Hungary, **6** Szentagothai Research Center, University of Pecs, Pecs, Hungary, **7** Department of Neurology, Odense University Hospital, Institute of Clinical Research, University of Southern Denmark, Odense, Denmark, **8** Department of Urology, University of Pecs, Pecs, Hungary

☯ These authors contributed equally to this work.
* zita.bognar@aok.pte.hu

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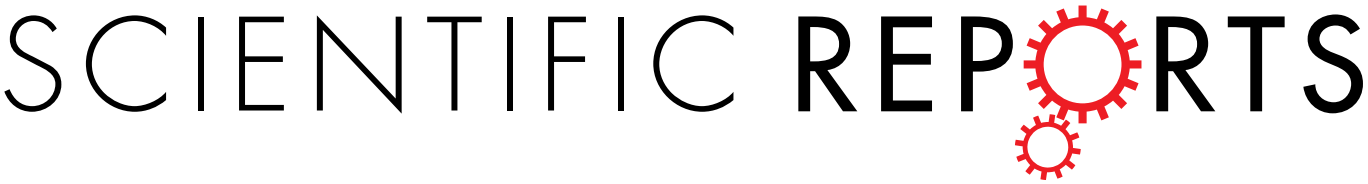
Abstract

Previous studies on the degenerative animal model of multiple sclerosis suggested that the copper-chelator cuprizone might directly suppress T-cell functions. Peripheral T-cell function in the cuprizone model has already been explored; therefore, in the present study, we investigated, for the first time, how cuprizone feeding affects the thymus, the organ of T-cell maturation and selection. We found that even one week of cuprizone treatment induced significant thymic atrophy, affecting the cortex over the medulla. Fluorescent microscopy and flow-cytometric analyses of thymi from cuprizone- and vehicle-treated mice indicated that eradication of the cluster of the differentiation-4 (CD4)-CD8 double-positive T-cell subset was behind the substantial cell loss. This result was confirmed with CD3-CD4-CD8 triple-staining experiments. Ultrastructurally, we observed degraded as well as enlarged mitochondria, myelin-bodies, large lipid droplets, and large lysosomes in the thymi of cuprizone-treated mice. Some of these features were similar to those in physiological and steroid-induced accelerated aging. According to our results, apoptosis was mainly of mitochondrial origin mediated by both caspase-3- and apoptosis inducing factor-mediated mechanisms. Additionally, mitogen activated protein kinase activation and increased pro-apoptotic B cell lymphoma-2 family protein expression were the major underlying processes. Our results do not indicate a functional relationship between cuprizone-induced thymus involution and the absence of inflammatory responses or the selective demyelination observed in the cuprizone model. On the other hand, due to the reversible nature of cuprizone's deleterious effects, the cuprizone model could be valuable in studying thymus regeneration as well as remyelination processes.



OPEN

The scaffold protein Tks4 is required for the differentiation of mesenchymal stromal cells (MSCs) into adipogenic and osteogenic lineages

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Metta Dülk[1,*], Gyöngyi Kudlik[1,*], Anna Fekete[1], Dávid Ernszt[2,3], Krisztián Kvell[2,3], Judit E. Pongrácz[2,3], Balázs L. Merő[1], Bálint Szeder[1], László Radnai[1], Miklós Geiszt[4,5], Dalma E. Csécsy[1], Tamás Kovács[1], Ferenc Uher[6], Árpád Lányi[7], Virag Vas[1] & László Buday[1,8]

The commitment steps of mesenchymal stromal cells (MSCs) to adipogenic and other lineages have been widely studied but not fully understood. Therefore, it is critical to understand which molecules contribute to the conversion of stem cells into differentiated cells. The scaffold protein Tks4 plays a role in podosome formation, EGFR signaling and ROS production. Dysfunction of Tks4 causes a hereditary disease called Frank-ter Haar syndrome with a variety of defects concerning certain mesenchymal tissues (bone, fat and cartilage) throughout embryogenic and postnatal development. In this study, we aimed to analyze how the mutation of Tks4 affects the differentiation potential of multipotent bone marrow MSCs (BM-MSCs). We generated a Tks4 knock-out mouse strain on C57Bl/6 background, and characterized BM-MSCs isolated from wild type and Tks4$^{-/-}$ mice to evaluate their differentiation. Tks4$^{-/-}$ BM-MSCs had reduced ability to differentiate into osteogenic and adipogenic lineages compared to wild type. Studying the expression profile of a panel of lipid-regulated genes during adipogenic induction revealed that the expression of adipogenic transcription factors, genes responsible for lipid droplet formation, sterol and fatty acid metabolism was delayed or reduced in Tks4$^{-/-}$ BM-MSCs. Taken together, these results establish a novel function for Tks4 in the regulation of MSC differentiation.

Frank-ter Haar syndrome (FTHS, OMIM:249420), is a rare genetic disorder associated with skeletal defects, craniofacial anomalies, cardiovascular abnormalities and, in some cases, reduced lipoid tissue[1,2]. The majority of FTHS patients die in infancy or in early childhood due to cardiovascular symptoms or respiratory infections[3]. The most common underlying genetic defects in FTHS have been recently identified through homozygosity mapping studies in patients, identifying homozygous mutations in the *SH3PXD2B* gene on chromosome 5q35.1[3]. The analysis of patients detected 4 different intragenic mutations, and one complete deletion of *SH3PXD2*[3]. A novel mutation in FTHS patients has also been described as the deletion of exon 13 of the *SH3PXD2B* gene[4]. Recently, two new homozygous loss-of-function mutations were identified in the *SH3PXD2B* gene in patients with Borrone dermato-cardio-skeletal syndrome (BDSC syndrome) which is a FTHS related genetic disease[5].

[1]Institute of Enzymology, Research Centre for Natural Sciences, Hungarian Academy of Sciences, Budapest, Hungary. [2]Department of Pharmaceutical Biotechnology, Faculty of Pharmacy, University of Pecs, Hungary. [3]Szentagothai Research Center, University of Pecs, Hungary. [4]Department of Physiology, Semmelweis University Medical School, Budapest, Hungary. [5]"Momentum" Peroxidase Enzyme Research Group of the Semmelweis University and the Hungarian Academy of Sciences, Budapest, Hungary. [6]Stem Cell Biology, National Blood Service, Budapest, Hungary. [7]Department of Immunology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary. [8]Department of Medical Chemistry, Semmelweis University Medical School, Budapest, Hungary. *These authors contributed equally to this work. Correspondence and requests for materials should be addressed to V.V. (email: vas.virag@ttk.mta.hu)

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PPARgamma Deficiency Counteracts Thymic Senescence

*David Ernszt[1,2], Krisztina Banfai[1,2], Zoltan Kellermayer[3], Attila Pap[4], Janet M. Lord[5], Judit E. Pongracz[1,2] and Krisztian Kvell[1,2]**

[1] Faculty of Pharmacy, Department of Pharmaceutical Biotechnology, University of Pecs, Pecs, Hungary, [2] Szentagothai Research Center, University of Pecs, Pecs, Hungary, [3] Faculty of Medicine, Department of Immunology and Biotechnology, University of Pecs, Pecs, Hungary, [4] Faculty of Medicine, Department of Biochemistry and Molecular Biology, University of Debrecen, Debrecen, Hungary, [5] College of Medical and Dental Sciences, Institute of Inflammation and Aging, University of Birmingham, Birmingham, United Kingdom

Thymic senescence contributes to increased incidence of infection, cancer and autoimmunity at senior ages. This process manifests as adipose involution. As with other adipose tissues, thymic adipose involution is also controlled by PPARgamma. This is supported by observations reporting that systemic PPARgamma activation accelerates thymic adipose involution. Therefore, we hypothesized that decreased PPARgamma activity could prevent thymic adipose involution, although it may trigger metabolic adverse effects. We have confirmed that both human and murine thymic sections show marked staining for PPARgamma at senior ages. We have also tested the thymic lobes of PPARgamma haplo-insufficient and null mice. Supporting our working hypothesis both adult PPARgamma haplo-insufficient and null mice show delayed thymic senescence by thymus histology, thymocyte mouse T-cell recombination excision circle qPCR and peripheral blood naive T-cell ratio by flow-cytometry. Delayed senescence showed dose–response with respect to PPARgamma deficiency. Functional immune parameters were also evaluated at senior ages in PPARgamma haplo-insufficient mice (null mice do not reach senior ages due to metabolic adverse affects). As expected, sustained and elevated T-cell production conferred oral tolerance and enhanced vaccination efficiency in senior PPARgamma haplo-insufficient, but not in senior wild-type littermates according to ELISA IgG measurements. Of note, humans also show increased oral intolerance issues and decreased protection by vaccines at senior ages. Moreover, PPARgamma haplo-insufficiency also exists in human known as a rare disease (FPLD3) causing metabolic adverse effects, similar to the mouse. When compared to age- and metabolic disorder-matched other patient samples (FPLD2 not affecting PPARgamma activity), FPLD3 patients showed increased human Trec (hTrec) values by qPCR (within healthy human range) suggesting delayed thymic senescence, in accordance with mouse results and supporting our working hypothesis. In summary, our experiments prove that systemic decrease of PPARgamma activity prevents thymic senescence, albeit with metabolic drawbacks. However, thymic tissue-specific PPARgamma antagonism would likely solve the issue.

Keywords: PPARgamma, thymus, immunity, senescence, rejuvenation

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****Correspondence:***
Krisztian Kvell
kvell.krisztian@pte.hu

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Respiratory Research

REVIEW Open Access

WNT signaling – lung cancer is no exception

Judit Rapp[1,2], Luca Jaromi[1,2], Krisztian Kvell[1,2], Gyorgy Miskei[1,2] and Judit E. Pongracz[1,2*]

Abstract

Since the initial discovery of the oncogenic activity of WNT ligands our understanding of the complex roles for WNT signaling pathways in lung cancers has increased substantially. In the current review, the various effects of activation and inhibition of the WNT signaling pathways are summarized in the context of lung carcinogenesis. Recent evidence regarding WNT ligand transport mechanisms, the role of WNT signaling in lung cancer angiogenesis and drug transporter regulation and the importance of microRNA and posttranscriptional regulation of WNT signaling are also reviewed.

Background

Lung cancer (LC) is one of the deadliest forms of cancer worldwide [1, 2] affecting both genders [3, 4]. The two main types of LC-s are small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). SCLC represents 15–20% of all LC cases and is the more aggressive form; it metastasizes early and therefore surgical intervention is rarely a therapeutic option [5]. On the other hand, NSCLC denotes 80–85% and can be further classified into adeno (AC)-, squamous cell (SCC) -, large cell (LCC) and various mixed type carcinomas [6]. Unfortunately, the majority of NSCLC patients are diagnosed at an advanced stage of the disease narrowing down therapeutic options and leading to a limited median survival of about 18 months [7]. Recent studies have confirmed that therapy-surviving cancer stem cells (CSC) play a cardinal role in drug resistance and therefore, rapid progression of the disease [8]. While the carcinogenic process in the lung can be traced back to genetic mutations, malfunctioning signaling pathways are also highly important modulators of tumor formation and individual features of the disease.

An increasing amount of evidence has shown that the WNT pathway is one of the main signaling pathways involved in maintaining lung homeostasis and that aberrant activation of this pathway may underlie several debilitating lung diseases. Similarly, to other human cancers, WNT signaling plays an important part in lung carcinogenesis. Interestingly, however, while some epigenetic changes that affect WNT pathway inhibitors are similar to those seen in other malignancies, genetic mutations of the WNT pathway are uncommon in NSCLCs [9].

This review will summarize some novel aspects of WNT signaling, what is currently known about WNT associated LC pathogenesis as well as some important features of WNT mediated events in LC therapies.

The complexity of WNT signaling – Canonical and non-canonical WNT signaling pathways

WNT proteins are secreted glyco-lipoprotein morphogens that are required during lung development for cell-fate specification, cell proliferation and the control of asymmetric cell division. In adults, WNT signaling is essential for stem cell maintenance for regulation of tissue homeostasis [10]. Most of the 19 WNT ligands and the 10 main receptors, Frizzleds (FZD) that have been identified in mammalian cells can be identified in the human lung [9, 11]. The two main different WNT pathways include i) the beta-catenin-dependent or canonical pathway, and ii) the beta-catenin-independent or non-canonical pathways including the planar cell polarity (PCP) and the WNT/Ca2+ pathways (Fig. 1).

Canonical or beta-catenin dependent WNT signaling.

In the lung, the role of WNT signaling has been examined in detail by multiple studies which mostly focus on beta-catenin-dependent signaling. In the canonical pathway during the absence of WNT, a beta-catenin destruction

* Correspondence: pongracz.e.judit@pte.hu
[1]Department of Pharmaceutical Biotechnology, School of Pharmacy, University of Pecs, Pecs, Hungary
[2]Szentagothai Research Centre, University of Pecs, Pecs, Hungary

toxins

MDPI

Article

Effect of *Vipera ammodytes ammodytes* Snake Venom on the Human Cytokine Network

Francisc Boda [1], Krisztina Banfai [2,3], Kitti Garai [2,3], Augustin Curticapean [1], Lavinia Berta [1,*], Emese Sipos [4] and Krisztian Kvell [2,3]

1 Department of Fundamental Pharmaceutical Sciences, Faculty of Pharmacy, University of Medicine and Pharmacy of Tirgu Mures, Gheorghe Marinescu Street No. 38, 540139 Tirgu Mures, Romania; boda.francisc@umftgm.ro (F.B.); augustin.curticapean@umftgm.ro (A.C.)

2 Department of Pharmaceutical Biotechnology, Faculty of Pharmacy, University of Pecs, Rokus Street No. 2, 7624 Pecs, Hungary; krisztina.banfai@aok.pte.hu (K.B.); garai.kitti91@gmail.com (K.G.); kvell.krisztian@pte.hu (K.K.)

3 Szentagothai Research Center, University of Pecs, Ifjusag Street No. 20, 7624 Pecs, Hungary

4 Department of Specialty Pharmaceutical Sciences, Faculty of Pharmacy, University of Medicine and Pharmacy of Tirgu Mures, Gheorghe Marinescu Street No. 38, 540139 Tirgu Mures, Romania; emese.sipos@umftgm.ro

* Correspondence: grama.lavinia@umftgm.ro; Tel.: +40-740-694-638

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Abstract: Local inflammation is a well-known symptom of envenomation by snakes of the family *Viperidae*, attributed primarily to the phospholipase A_2s, metalloproteinases and L-amino acid oxidases contained in their venom. The inflammatory effect of snake venoms has been associated with a marked increase of the cytokines IL-1β, IL-6, IL-8, IL-10 and TNF-α. To determine the impact of *Vipera ammodytes ammodytes* snake venom on the expression of inflammation-related genes, we incubated human U937 monocyte cells with dilutions of snake venom. Gene expression was quantified for 28 different genes using a TaqMan® Array Human Cytokine Network 96-well Plate in a RT-qPCR system. Our results have demonstrated that 1.0 µg/mL *Vipera ammodytes ammodytes* venom solution induces a notable change in the expression of several cytokine network genes. Among the upregulated genes, there were several that encode interleukins, interferons, and tumor necrosis factors. We further report the downregulation of three interleukin-related genes. Our findings come as supportive information for the known complex effect of snake venoms on the human cytokine network. It also provides relevant new information regarding the expression of genes that have not been previously associated with the effect of snake venoms.

Keywords: snake venoms; *Vipera ammodytes*; inflammation-related genes; inflammatory mediators; cytokines; RT-qPCR

Key Contribution: We present a Taqman Array method to simultaneously determine the effect of *Vipera ammodytes ammodytes* snake venom on 28 inflammation-related genes. The results show that the venom alters the expression of several cytokine network genes, including genes not yet associated with the effect of snake venoms.

1. Introduction

The inflammatory process represents a defense mechanism of the body against harmful pathogens, damaged cells, or irritating substances. Inflammation can take an acute or chronic form. In its acute form, five typical signs of inflammation are usually present: heat, pain, redness, swelling, and loss of function of the affected tissues or organs. Chronic inflammatory processes are characterized by a

cells

MDPI

Article

Analysis of Tks4 Knockout Mice Suggests a Role for Tks4 in Adipose Tissue Homeostasis in the Context of Beigeing

Virag Vas [1,*], Tamás Háhner [1], Gyöngyi Kudlik [1], Dávid Ernszt [2], Krisztián Kvell [3], Dániel Kuti [4], Krisztina J. Kovács [4], József Tóvári [5], Mária Trexler [1], Balázs L. Merő [1], Bálint Szeder [1], Kitti Koprivanacz [1] and László Buday [1,6]

1 Institute of Enzymology, Research Centre for Natural Sciences, Hungarian Academy of Sciences, 1117 Budapest, Hungary
2 Institute of Physiology, Medical School University of Pécs, 7622 Pécs, Hungary
3 Department of Pharmaceutical Biotechnology, Faculty of Pharmacy and Szentagothai Research Center University of Pécs, 7622 Pécs, Hungary
4 Laboratory of Molecular Neuroendocrinology, Institute of Experimental Medicine, 1083 Budapest, Hungary
5 Department of Experimental Pharmacology, National Institute of Oncology, 1122 Budapest, Hungary
6 Department of Medical Chemistry, Semmelweis University Medical School, 1094 Budapest, Hungary
* Correspondence: vas.virag@ttk.mta.hu; Tel.: +36-20-210-0880

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Abstract: Obesity and adipocyte malfunction are related to and arise as consequences of disturbances in signaling pathways. Tyrosine kinase substrate with four Src homology 3 domains (Tks4) is a scaffold protein that establishes a platform for signaling cascade molecules during podosome formation and epidermal growth factor receptor (EGFR) signaling. Several lines of evidence have also suggested that Tks4 has a role in adipocyte biology; however, its roles in the various types of adipocytes at the cellular level and in transcriptional regulation have not been studied. Therefore, we hypothesized that Tks4 functions as an organizing molecule in signaling networks that regulate adipocyte homeostasis. Our aims were to study the white and brown adipose depots of Tks4 knockout (KO) mice using immunohistology and western blotting and to analyze gene expression changes regulated by the white, brown, and beige adipocyte-related transcription factors via a PCR array. Based on morphological differences in the Tks4-KO adipocytes and increased uncoupling protein 1 (UCP1) expression in the white adipose tissue (WAT) of Tks4-KO mice, we concluded that the beigeing process was more robust in the WAT of Tks4-KO mice compared to the wild-type animals. Furthermore, in the Tks4-KO WAT, the expression profile of peroxisome proliferator-activated receptor gamma (PPARγ)-regulated adipogenesis-related genes was shifted in favor of the appearance of beige-like cells. These results suggest that Tks4 and its downstream signaling partners are novel regulators of adipocyte functions and PPARγ-directed white to beige adipose tissue conversion.

Keywords: WAT browning; beige adipocytes; adipogenesis; Tks4 scaffold protein

1. Introduction

Obesity and obesity-related diseases are becoming increasingly common, and while the obesity-inducing effects of physical inactivity and poor eating habits are well known, other factors that contribute to the development of obesity and obesity-associated conditions are less clear [1]. Therefore, the molecular and genetic mechanisms governing obesity are intensively studied, with the goal of improving the management and treatment of obesity-associated diseases [2–4]. Such studies have identified numerous biochemical factors that control fat storage [5–7] and differences in

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"Beige" Cross Talk Between the Immune System and Metabolism

*Krisztina Banfai[1,2], David Ernszt[2,3], Attila Pap[4], Peter Bai[5,6,7,8], Kitti Garai[1,2], Djeda Belharazem[9], Judit E. Pongracz[1,2] and Krisztian Kvell[1,2]**

[1] Department of Pharmaceutical Biotechnology, Faculty of Pharmacy, University of Pécs, Pécs, Hungary, [2] Szentagothai Research Center, University of Pécs, Pécs, Hungary, [3] Department of Physiology, Medical School, University of Pécs, Pécs, Hungary, [4] Department of Biochemistry and Molecular Biology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary, [5] Medical Chemistry, Faculty of Medicine, University of Debrecen, Debrecen, Hungary, [6] MTA-DE Cell Biology and Signaling Research Group, Debrecen, Hungary, [7] MTA-DE Lendulet Laboratory of Cellular Metabolism, Debrecen, Hungary, [8] Research Center for Molecular Medicine, University of Debrecen, Debrecen, Hungary, [9] Department of Pathology, University Hospital of Mannheim, Mannheim, Germany

With thymic senescence the epithelial network shrinks to be replaced by adipose tissue. Transcription factor TBX-1 controls thymus organogenesis, however, the same TBX-1 has also been reported to orchestrate beige adipose tissue development. Given these different roles of TBX-1, we have assessed if thymic TBX-1 expression persists and demonstrates this dualism during adulthood. We have also checked whether thymic adipose involution could yield beige adipose tissue. We have used adult mouse and human thymus tissue from various ages to evaluate the kinetics of TBX-1 expression, as well as mouse (TEP1) and human (1889c) thymic epithelial cells (TECs) for our studies. Electron micrographs show multi-locular lipid deposits typical of beige adipose cells. Histology staining shows the accumulation of neutral lipid deposits. qPCR measurements show persistent and/or elevating levels of beige-specific and beige-indicative markers (TBX-1, EAR-2, UCP-1, PPAR-gamma). We have performed miRNome profiling using qPCR-based QuantStudio platform and amplification-free NanoString platform. We have observed characteristic alterations, including increased miR21 level (promoting adipose tissue development) and decreased miR34a level (bias toward beige adipose tissue differentiation). Finally, using the Seahorse metabolic platform we have recorded a metabolic profile (OCR/ECAR ratio) indicative of beige adipose tissue. In summary, our results support that thymic adipose tissue emerging with senescence is *bona fide* beige adipose tissue. Our data show how the borders blur between a key immune tissue (the thymus) and a key metabolic tissue (beige adipose tissue) with senescence. Our work contributes to the understanding of cross talk between the immune system and metabolism.

Keywords: thymus senescence, beige adipose tissue, TBX-1, UCP-1, PPARgamma

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Jie Chen,
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Lluis Tort,
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Mark Klitgaard Nøhr,
University of Copenhagen, Denmark

****Correspondence:***
Krisztian Kvell
kvell.krisztian@pte.hu

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INTRODUCTION

In human the degenerative process of thymic adipose involution is already detectable in childhood and accelerates with puberty due to hormonal (sex-steroid) induction (1–3). The process shows identical kinetics in mouse. Also, we have developed a model whereby TECs are treated by a steroid (using Dx or dexamethasone) thus both *in vivo* and *in vitro* model systems are readily available (4) As for all adipose tissues subtypes, thymic adipose involution is orchestrated by transcription

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Transgenic Exosomes for Thymus Regeneration

Krisztina Banfai[1,2], *Kitti Garai*[1,2], *David Ernszt*[2,3], *Judit E. Pongracz*[1,2] *and Krisztian Kvell*[1,2]*

[1] Department of Pharmaceutical Biotechnology, Faculty of Pharmacy, University of Pécs, Pécs, Hungary, [2] Szentagothai Research Center, University of Pécs, Pécs, Hungary, [3] Faculty of Medicine, Institute of Physiology, University of Pécs, Pécs, Hungary

During senescence, Wnt4 expression is down-regulated (unlike their Frizzled receptors), while PPARgamma expression increases in the thymus. Together, these changes allow for thymic degeneration to occur, observed as adipose involution. However, when restored, Wnt4 can efficiently counteract PPARgamma and prevent thymic senescence from developing. The Wnt-pathway activator miR27b has also been reported to inhibit PPARgamma. Our goal was to evaluate the Wnt4 and miR27b levels of Wnt4-transgenic thymic epithelial cell (TEC)-derived exosomes, show their regenerative potential against age-related thymic degeneration, and visualize their binding and distribution both *in vitro* and *in vivo*. First, transgenic exosomes were harvested from Wnt4 over-expressing TECs and analyzed by transmission electron microscopy. This unveiled exosomes ranging from 50 to 100 nm in size. Exosomal Wnt4 protein content was assayed by ELISA, while miR27b levels were measured by TaqMan qPCR, both showing elevated levels in transgenic exosomes relative to controls. Of note, kit-purified TEI (total exosome isolate) outperformed UC (ultracentrifugation)-purified exosomes in these parameters. In addition, a significant portion of exosomal Wnt4 proved to be displayed on exosomal surfaces. For functional studies, steroid (Dexamethasone or DX)-induced TECs were used as cellular aging models in which DX-triggered cellular aging was efficiently prevented by transgenic exosomes. Finally, DiI lipid-stained exosomes were applied on the mouse thymus sections and also iv-injected into mice, for *in vitro* binding and *in vivo* tracking, respectively. We have observed distinct staining patterns using DiI lipid-stained transgenic exosomes on sections of young and aging murine thymus samples. Moreover, *in vivo* injected DiI lipid-stained transgenic exosomes showed detectable homing to the thymus. Of note, Wnt4-transgenic exosome homing outperformed control (Wnt5a-transgenic) exosome homing. In summary, our findings indicate that exosomal Wnt4 and miR27b can efficiently counteract thymic adipose involution. Although extrapolation of mouse results to the human setting needs caution, our results appoint transgenic TEC exosomes as promising tools of immune rejuvenation and contribute to the characterization of the immune-modulatory effects of extracellular vesicles in the context of regenerative medicine.

Keywords: aging, thymus, exosome, Wnt4, miR27b

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Denise Doolan,
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University of Hawaii at Manoa, United States
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Hungarian Academy of Sciences, Hungary

***Correspondence:**
Krisztian Kvell
kvell.krisztian@pte.hu

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Artificial Neural Network Correlation and Biostatistics Evaluation of Physiological and Molecular Parameters in Healthy Young Individuals Performing Regular Exercise

Kitti Garai[1,2], Zoltan Adam[1,2], Robert Herczeg[3], Emese Katai[2,4], Tamas Nagy[2,4], Szilard Pal[5], Attila Gyenesei[3], Judit E. Pongracz[1,2], Marta Wilhelm[6] and Krisztian Kvell[1,2]*

[1] Department of Pharmaceutical Biotechnology, Faculty of Pharmacy, University of Pécs, Pécs, Hungary, [2] Wnt Signaling Research Group, Szentagothai Research Center, University of Pécs, Pécs, Hungary, [3] Bioinformatics Research Group, Szentagothai Research Center, University of Pécs, Pécs, Hungary, [4] Department of Laboratory Medicine, University of Pécs, Pécs, Hungary, [5] Department of Pharmaceutical Technology and Biopharmacy, Faculty of Pharmacy, University of Pécs, Pécs, Hungary, [6] Faculty of Science, Institute of Sport Sciences and Physical Education, University of Pécs, Pécs, Hungary

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Giuseppe D'Antona, University of Pavia, Italy

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Garry Kuan, Universiti Sains Malaysia, Malaysia
Ildiko Bock-Marquette, University of Pécs, Hungary

***Correspondence:**
Marta Wilhelm
mwilhelm@gamma.ttk.pte.hu

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Studies support that regular physical activity (PA) decelerates senescence-related decline of physiological and molecular parameters in the elderly. We have addressed the other end of this spectrum: healthy and young, inactive individuals participated in a 6-month long personal trainer-guided lifestyle program. We have measured physiological and molecular parameters (differentiating high- and low responders) and their correlation with PA (sedentary status). Cluster analysis helped to distinguish individuals with high- or low PA and differentiate high- and low-responders of each parameter. The assessed cardiovascular parameters (heart rate, blood pressure, 6-min walking distance, relative VO_2max), body composition parameters (body fat and muscle mass percentage) metabolic parameters (glucose, insulin, HDL, LDL), immune parameters (cortisol, CRP, lymphocyte counts, hTREC) all showed improvement. Artificial neural network analysis (ANN) showed correlation efficiencies of physiological and molecular parameters using a concept-free approach. ANN analysis appointed PA as the mastermind of molecular level changes. Besides sedentary status, insulin and hTREC showed significant segregation. Biostatistics evaluation also supported the schism of participants for their sedentary status, insulin concentration and hTREC copy number. In the future ANN and biostatistics, may predict individual responses to regular exercise. Our program reveals that high responder individuals of certain parameters may be low responders of others. Our data show that moderate regular PA is essential to counteract senescence in young and healthy individuals, despite individual differences in responsiveness. Such PA may not seem important in the everyday life of young and healthy adults, but shall become the base for healthy aging.

Keywords: aging, physical activity, responsiveness, prediction, prevention

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Effect of *Bitis gabonica* and *Dendroaspis angusticeps* snake venoms on apoptosis-related genes in human thymic epithelial cells

Francisc Boda[1], Krisztina Banfai[2,3], Kitti Garai[2,3], Bela Kovacs[1*], Attila Almasi[4], Dalma Scheffer[3,5], Reka Lambertne Sinkler[3,5], Robert Csonka[3,5], Tamas Czompoly[3,5], Krisztian Kvell[2,3]

[1]Department F1, Faculty of Pharmacy, George Emil Palade University of Medicine, Pharmacy, Science, and Technology of Targu Mures, Targu Mures, Romania.
[2]Department of Pharmaceutical Biotechnology, Faculty of Pharmacy, University of Pecs, Pecs, Hungary.
[3]Food Biotechnology Research Group, Szentagothai Research Center, University of Pecs, Pecs, Hungary.
[4]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Pecs, Pecs, Hungary.
[5]Soft Flow Ltd., Pecs, Hungary.

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Abstract

Background: Certain environmental toxins permanently damage the thymic epithelium, accelerate immune senescence and trigger secondary immune pathologies. However, the exact underlying cellular mechanisms and pathways of permanent immune intoxication remain unknown. The aim of the present study was to demonstrate gene expressional changes of apoptosis-related cellular pathways in human thymic epithelial cells following exposure to snake venom from *Bitis gabonica* and *Dendroaspis angusticeps*.

Methods: Snake venoms were characterized by analytical methods including reversed phase high-performance liquid chromatography and sodium dodecyl sulphate-polyacrylamide gel electrophoresis, then applied on human thymic epithelial cells (1889c) for 24 h at 10 µg/mL (as used in previous TaqMan Array study). Gene expressional changes restricted to apoptosis were assayed by TaqMan Array (Human Apoptosis Plate).

Results: The most prominent gene expressional changes were shown by *CASP5* (≈ 2.5 million-fold, confirmed by dedicated quantitative polymerase chain reaction) and *CARD9* (0.016-fold) for *B. gabonica*, and *BIRC7* (6.46-fold) and *CASP1* (0.30-fold) for *D. angusticeps*.

Conclusion: The observed apoptotic environment suggests that pyroptosis may be the dominant pathway through which *B. gabonica* and *D. angusticeps* snake venoms trigger thymic epithelial apoptosis following envenomation.

*** Correspondence:** bela.kovacs@umfst.ro
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Physical Activity as a Preventive Lifestyle Intervention Acts Through Specific Exosomal miRNA Species—Evidence From Human Short- and Long-Term Pilot Studies

*Kitti Garai[1,2], Zoltan Adam[1,2], Robert Herczeg[3], Krisztina Banfai[1,2], Adam Gyebrovszki[4], Attila Gyenesei[3], Judit E. Pongracz[1,2], Marta Wilhelm[4] and Krisztian Kvell[1,2]**

[1] Department of Pharmaceutical Biotechnology, Faculty of Pharmacy, University of Pécs, Pécs, Hungary, [2] Wnt-Signaling Research Group, Szentagothai Research Center, University of Pécs, Pécs, Hungary, [3] Bioinformatics Research Group, Szentagothai Research Center, University of Pécs, Pécs, Hungary, [4] Faculty of Science, Institute of Sport Sciences and Physical Education, University of Pécs, Pécs, Hungary

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Martin Burtscher, University of Innsbruck, Austria

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Shamila D. Alipoor, National Institute for Genetic Engineering and Biotechnology, Iran
Sigrun Lange, University of Westminster, United Kingdom

***Correspondence:**
Krisztian Kvell
kvell.krisztian@pte.hu

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Exercise initiates systemic adaptation to promote health and prevent various lifestyle-related chronic diseases. Emerging evidence suggests that circulating exosomes mediate some of the beneficial effects of exercise via the transfer of microRNAs between tissues. Yet to date, a comprehensive profile of the exosomal miRNA (exomiR) content released following short-term (0.5 year in this study) and long-term (25 + years in this study) regular bouts of exercise is still lacking. However, a better understanding of these miRNA species would assist in clarifying the role of regular exercise at the molecular level in the prevention of chronic diseases. In the present pilot studies we analyzed serum exomiR expression in healthy young, sedentary participants (n = 14; age: 23 ± 2 years) at baseline and following a half year-long moderate-intensity regular exercise training. We also analyzed serum exomiR expression in older, healthy trained participants (seniors, n = 11; age: 62 ± 6 years) who engaged in endurance activities for at least 25 years. Following the isolation and enrichment of serum exosomes using Total Exosome Isolation Reagent (TEI) their exomiR levels were determined using the amplification-free Nanostring platform. Hierarchical cluster analysis revealed that the majority of exomiRs overlap for short-term (0.5 year in this study) and long-term (25 + years in this study) regular bouts of exercise. The top 12 significantly altered exomiRs (let-7a-5p; let-7g-5p; miR-130a-3p; miR-142-3p; miR-150-5p; miR-15a-5p; miR-15b-5p; miR-199a-3p; miR-199b-3p; miR-223-3p; miR-23a-3p, and miR-451a-3p) were used for further evaluation. According to KEGG pathway analysis a large portion of the exomiRs target chronic diseases including cancer, neurodegenerative and metabolic diseases, and viral infections. Our results provide evidence that exosomal miRNA modulation is the molecular mechanism through which regular exercise prevents various chronic diseases. The possibility of using such exomiRs to target diseases is of great interest. While further validation is needed, our comprehensive exomiR study presents, for the first time, the disease-preventive molecular pattern of both short and long-term regular exercise.

Keywords: regular exercise, exosome, miRNA, chronic disease, prevention

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EDITED BY
Paul Takam Kamga,
Universitéde Versailles Saint-Quentin-en-Yvelines, France

REVIEWED BY
Hiroaki Toba,
Tokushima University, Japan
Agnese Po,
Sapienza University of Rome, Italy

*CORRESPONDENCE
Djeda Belharazem
djeda.belharazem@medma.uni-heidelberg.de

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WNT4 overexpression and secretion in thymic epithelial tumors drive an autocrine loop in tumor cells *in vitro*

Xiaonan Zhang[1], Berthold Schalke[2], Krisztian Kvell[3], Katharina Kriegsmann[4], Mark Kriegsmann[5,6], Thomas Graeter[7], Gerhard Preissler[8], German Ott[9,10], Katrin Kurz[9,10], Elena Bulut[11], Philipp Ströbel[12], Alexander Marx[1] and Djeda Belharazem[1*]

[1]Institute of Pathology and Medical Research Center, University Medical Centre Mannheim, University of Heidelberg, Mannheim, Germany, [2]Department of Neurology, University of Regensburg, Regensburg, Germany, [3]Department of Pharmaceutical Biotechnology, Faculty of Pharmacy, University of Pecs, Pecs, Hungary, [4]Department of Hematology, Oncology and Rheumatology, University Hospital Heidelberg, Heidelberg, Germany, [5]Translational Lung Research Centre Heidelberg, German Centre for Lung Research, Heidelberg, Germany, [6]Institute of Pathology, University Hospital Heidelberg, Heidelberg University, Heidelberg, Germany, [7]Department of Thoracic Surgery, University Medical Centre Erlangen, Erlangen, Germany, [8]Department of Thoraxic Surgery, Clinic Schillerhöhe, Robert-Bosch-Hospital, Gerlingen, Löwenstein, Germany, [9]Department of Clinical Pathology, Robert-Bosch-Hospital, Stuttgart, Germany, [10]Dr. Margarete Fischer-Bosch Institute for Clinical Pharmacology, Robert-Bosch-Hospital, Stuttgart, Germany, [11]Department of Thoraxic Surgery, Thoraxklinik at Heidelberg University Hospital, Heidelberg, Germany, [12]Institute of Pathology, University Medical Center Göttingen, University of Göttingen, Göttingen, Germany

Background: WNT4-driven non-canonical signaling is crucial for homeostasis and age-related involution of the thymus. Abnormal WNT signaling is important in many cancers, but the role of WNT signaling in thymic tumors is largely unknown.

Materials & Methods:: Expression and function of WNT4 and FZD6 were analyzed using qRT–PCR, Western blot, ELISA, in biopsies of non-neoplastic thymi (NT), thymoma and thymic carcinomas. ShRNA techniques and functional assays were used in primary thymic epithelial cells (pTECs) and TC cell line 1889c. Cells were conventionally (2D) grown and in three-dimensional (3D) spheroids.

Results: In biopsy, WHO classified B3 thymomas and TCs showed increased WNT4 expression compared with NTs. During short-term 2D culture, WNT4 expression and secretion declined in neoplastic pTECs but not in 3D spheroids or medium supplemented with recombinant WNT4 cultures. Under the latter condition, the growth of pTECs was accompanied by increased expression of non-canonical targets RAC1 and JNK. Down-regulation of WNT4 by shRNA induced cell death in pTECs derived from B3 thymomas and led to decreased RAC1, but not JNK protein phosphorylation. Pharmacological inhibition of NF-κB decreased both RAC1 and JNK phosphorylation in neoplastic pTECs.

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Central Immune Senescence, Reversal Potentials

Krisztian Kvell and Judit E. Pongracz
Department of Medical Biotechnology, University of Pecs, Hungary

1. Introduction

1.1 Ageing in focus

Ageing is a complex process that affects all living organisms. Senescence is not only conceivable in multicellular organisms, but also in unicellulars. Unlike certain diseases that have specific morbidity rates, ageing is a physiological process that affects all individuals that live long enough (unaffected by i.e. predation or famine) to experience senescence.

A pioneer of ageing research, August Weismann has established two rather opposing concepts for aging and even today both gather numerous followers. One is the adaptive concept, according to which ageing has evolved to cleanse the population from old, non-reproductive consumers. The other, non-adaptive concept suggests that ageing is due to greater weight on early survival / reproduction rather than vigour at later ages. This latter has been reshaped by the theory of antagonistic pleiotropy (Ljubuncic et al. 2009).

Due to advances in biomedical research and care, currently an average 55-aged person is expected to live up to 85 years of age at death on average in the Western societies. This number is expected to increase if biomedical research continues to develop at the current rate and by the year 2030 an average 55-aged person is expected to live up to 115 years of age at death (according to SENS plans) (de Grey 2007). If such forecasts prove to be true, it is of extraordinary significance and will likely trigger immense social and economical conflicts.

1.1.1 Ageing and society

Ageing of the population is one of the most important challenges for the developed world to face over the next decades. The current demographic trends and consequent shrinkage of the active workforce will put enormous pressure on the financing of social protection and health systems, likely to reduce living standards. Taken together with increased migration and emergence of novel infectious diseases, broad-scale provision of immunological protection constitutes a strategic aim for longer and healthier lifespan.

At present life-span is still significantly increasing in the Western civilisations, however, this increase is not accompanied by proportional increase in life spent in overall good health referred to as 'health-span'. There are current efforts to prolong health-span within expanding life-span. This would not only extend life spent in appropriate quality of life, but

Immunosenescence and the Ageing Lung

6

Krisztian Kvell and Judit E. Pongracz

Abstract

Ageing is generally defined as the progressive decline of homeostasis that occurs after the reproductive phase of life is complete and the "*soma becomes disposable*" and death is inevitable according to one theory of ageing. The complexity of the ageing process becomes strikingly evident in the lung where tissue maintenance and repair suffer from damage at the genetic level as well as tissue level. Moreover, lung function declines steadily in adulthood and if data for older adults are extrapolated, the outcome suggests an upper age limit beyond which life becomes impossible. In this review we cover the main changes to lung structure and function with age and the impact on respiratory health. We also describe the role that an aged immune system may play in the age-related decline in lung function and the major involvement of altered signalling through developmental pathways with special focus on PPARγ.

Keywords

Lung function • Inflammation • PPARγ • Wnt • Ageing

6.1 Introduction

In a recent article [1] the association of age with lung function decline was summarized and showed a linear decline from maturity. If trajectories depicted in the paper are extrapolated (Fig. 6.1), it becomes evident that the absolute extent of human life is limited, at least in part, by respiratory function to about 130 years but currently there are no confirmed cases available of people who lived to the absolute limit of pulmonary functional decline. A rare exception is Mrs Tuti Yusupova of Uzbekistan who died in 2014 apparently at the age of 134 [2]. Although caution is

K. Kvell • J.E. Pongracz (✉)
Department of Pharmaceutical Biotechnology, School of Pharmacy, and Szentagothai Research Center, University of Pecs, 2 Rokus Str, Pecs 7624, Hungary
e-mail: pongracz.e.judit@pte.hu

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Chapter

Thymic Senescence

Krisztian Kvell

Abstract

Thymic senescence develops in every person, although at different pace. Thymic senescence significantly lowers the production of naive T cells, leading to increased incidence of infections, cancer and autoimmune diseases. Certain external factors can accelerate thymic senescence. These include chemicals (copper-chelators), hormones (androgens), infections (viruses, fungi, protozoa). Others may slow the aging process of the thymus including perturbations to the hormonal (sex-steroid) system, genetic alterations (PPARgamma deficiency) or chemical compounds (PPARgamma antagonists). Thymic senescence research may provide insight to underlying molecular events and potentially appoint novel therapeutic targets for senescence intervention strategies. These hold promise to postpone thymus senescence and enhance T cell production. That would result in a decreased incidence of infections, cancer and autoimmune diseases, currently affecting the elderly. The attributed drop in healthcare costs and gain in quality of life share tremendous economic and social interest.

Keywords: thymus, senescence, adipose tissue

1. The aging thymus

Transcription factor TBX-1 is a mastermind in the formation of the third pharyngeal pouch involved in thymus organogenesis during embryonic development [1]. Patients with 22q11.2DS that impairs TBX-1 often present thymus hypoplasia. Similarly, Tbx-1^{null} mice develop hypoplasia of the thymus [2, 3]. In both cases, defective thymus organogenesis leads to impaired thymocyte development [4]. However, as reported recently, the role of TBX-1 in thymus organogenesis is not straightforward. Ectopic forced expression of TBX-1 can inhibit transcription factor FoxN1, the mastermind of thymic epithelial identity thus indirectly impair thymus identity via sustained presence [5]. The thymus contains developing T cells (aka thymocytes) along with the non-lymphoid thymic stromal elements comprising the microenvironment that promotes thymocyte differentiation. Stromal elements include thymic epithelial cells (aka TECs), mesenchymal cells, endothelial cells as well as non-lymphoid hematopoietic cells (e.g., dendritic cells or macrophages). TECs constitute the main functional stromal cell type necessary to promote thymocyte differentiation [6, 7]. Soon after birth the thymus expands to increase the output of naive T cells, in order to colonize available niches in the periphery [8–10]. Cortical TECs (aka cTECs) are required for T lineage commitment, along with thymocyte expansion and differentiation, and positive selection. Medullary TECs (mTECs) are necessary for the induction of central tolerance and subsequent stages of thymocyte maturation before leaving the thymus. Of note, in order to maintain the well organized cortical and medullary compartments active (reverse) intercellular signaling is also required from developing thymocytes towards TECs