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Review article

Here, there and everywhere: Resistin-like molecules in infection, inflammation, and metabolic disorders

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ABSTRACT

The Resistin-Like Molecules (RELM) α, β, and γ and their namesake, resistin, share structural and sequence homology but exhibit significant diversity in expression and function within their mammalian host. RELM proteins are expressed in a wide range of diseases, such as: microbial infections (eg. bacterial and helminth), inflammatory diseases (eg. asthma, fibrosis) and metabolic disorders (eg. diabetes). While the expression pattern and molecular regulation of RELM proteins are well characterized, much controversy remains over their proposed functions, with evidence of host-protective and pathogenic roles. Moreover, the receptors for RELM proteins are unclear, although three receptors for resistin, decorin, adenylyl cyclase-associated protein 1 (CAP1), and Toll-like Receptor 4 (TLR4) have recently been proposed. In this review, we will first summarize the molecular regulation of the RELM gene family, including transcription regulation and tissue expression in humans and mouse disease models. Second, we will outline the function and receptor-mediated signaling associated with RELM proteins. Finally, we will discuss recent studies suggesting that, despite early misconceptions that these proteins are pathogenic, RELM proteins have a more nuanced and potentially beneficial role for the host in certain disease settings.

1. Introduction

Resistin-like molecules (RELMs) are mammalian secreted proteins, which were identified less than 20 years ago in different disease settings, leading to differing nomenclature [1–6]. RELMα (*Retnla*) was the first RELM protein discovered in a mouse model of asthma, where it was named FIZZ1 for Found in Inflammatory Zone. Murine resistin (*Retn*/FIZZ3) was subsequently identified and functionally characterized in metabolic dysfunction, where it caused "resistance" to insulin, leading to the more common nomenclature for this protein family as 'RELMs'. Finally, RELMα was also investigated in hypoxia and named Hypoxia-Induced Mitogenic Factor (HIMF) [1]. The complex nomenclature demonstrates significant diversity in RELM expression pattern and function, however, it may cause confusion and potential bias when searching for studies on this intriguing family of proteins. Here, we provide a comprehensive summary of the RELM/FIZZ/HIMF protein family, from their discovery to more recent studies elucidating their function and putative receptors.

We will focus on the three main research areas in which RELM proteins were discovered, which include microbial infection, inflammatory diseases and metabolic dysfunction. In addition, we will highlight the existing controversies over the pathogenic versus

Abbreviations: ABC, ATP-binding cassette transporter; ADD1, adipocyte determination and differentiation dependent factor 1; ADSF, adipocyte secreted factor; Akt (aka PKB), protein kinase B; AP1, activator protein 1; ASC, adipose stromal cells; BTK, Bruton's tyrosine kinase; C/EBP, CCAAT/enhancer-binding protein; cAMP, cyclic AMP; CAP1, adenylyl cyclase-associated protein 1; CCL2, chemokine (C-C motif) ligand 2; CD, cluster of differentiation; Cdx2, caudal type homeobox 2; CREB, cAMP-response element-binding protein; Cyp7a1, cholesterol 7 alpha-hydroxylase; Cyp8b1, sterol 12α-hydroxylase; DCN, decorin; DSS, dextran sulfate sodium; ERK, extracellular-signal-regulated kinase; Ets, E26 transformation-specific; FIZZ, found in inflammatory zone; GAS, gamma interferon activation site; GLUT4, glucose transporter 4; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HIMF, hypoxia-induced mitogenic factor; HL-60, human leukemia cells; HMGB, high mobility group box; HNF, hepatocyte nuclear factor; IBD, inflammatory bowel disease; IL, interleukin; IP_3R, inositol 1,4,5-triphosphate receptor; IRF1/2, interferon regulatory factor 1/2; IRS, insulin receptor substrate; JAK, Janus kinase; JNK, c-Jun N-terminal kinase; LPS, lipopolysaccharide; LRH-1, liver receptor homolog-1; M1, classically activated macrophage; M2, alternatively activated macrophage; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemotactic protein-1; MyD88, myeloid differentiation primary response 88; NF-κB, nuclear factor κB; PI3K, phosphoinositide 3-kinase; PKA, protein kinase A; PPAR, peroxisome activated receptor; PPRE, PPAR response element; RELM, resistin-like molecule; RXR, retinoid x receptor; SDF-1, stromal cell-derived factor 1; SNP, single nucleotide polymorphism; SOCS, suppressor of cytokine signaling; Sp, stimulatory proteins; SREBP1c, sterol regulatory element binding protein 1c; STAT, signal transducer and activator of transcription; TBK1, serine/threonine-protein kinase 1; Th1, T helper cell type 1; Th2, T helper cell type 2; Th17, T helper cell type 17; TLR, toll-like receptor; TNF-α, tumor necrosis factor alpha; Treg, regulatory T cell; TRIF, TIR domain-containing adaptor protein-inducing interferon β; VEGF, vascular endothelial factor; α-SMA, α-smooth muscle actin

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protective function for these proteins. While early studies proposed detrimental roles for RELM proteins due to their abundant expression in pathologic settings, more recent studies suggest that these proteins can provide beneficial functions from improving metabolic homeostasis to reducing inflammation and promoting wound healing. Here, we revisit the literature on RELM proteins to (i) consolidate what is known regarding RELM genetic regulation and signaling; and (ii) delineate the function of each RELM in various disease states. We hope to highlight the versatility of these proteins and the significant role they play in host physiology. Only by fully understanding RELMs in their respective roles within their host, can we make informed decisions on the possibility of targeting these molecules and downstream pathways for new therapies in infection, inflammation and metabolic dysfunction.

2. Molecular regulation of RELM genes

2.1. RELM gene and protein structure

The RELM gene family (*Retn*) was originally identified in mice, but appears to be present in all mammals [2]. While mice and rats have four RELM genes *Retn*, *Retnla*, *Retnlb*, *Retnlg*; only *Retn* and *Retnlb* belong to a diverse taxonomic group, including humans, nonhuman primates, canines, cats and horses. In mice and rats, three of the four RELM genes, *Retnlb*, *Retlna* and *Retnlg*, are clustered together on chromosome 16 [3]. These genes share the most sequence homology and exhibit similar transcriptional regulation, but are differentially expressed in cell-types and tissue. In comparison, mouse *Retn*, human *Retn* and human *Retnlb* exhibit greater diversity in transcriptional regulation and expression pattern, and are present on different chromosomes (chromosomes 8, 19 and 3 respectively). Sequence identity is high between human and mouse RELM proteins, with ~60% homology in amino acid sequence [4,5]. Fig. 1 summarizes the gene expression profile and transcriptional regulation of mouse and human RELM genes.

RELM genes encode secreted proteins of 105–138 amino acids in size with 3 main domains: an amino (N) terminal signal sequence, a variable middle section, and a conserved carboxyl (C) terminal. The C terminal is comprised of a cysteine signature motif sequence shared by all RELM family members (C-X_{11}-C-X_8-C-X-C-X_3-C-X_{10}-C-X-C-X-C-X_9-CC-X_{3-6}-END), which is proposed to be critical for disulfide bond formation and protein folding [3,6,7]. The crystal structures of mouse resistin and RELMβ have been solved, revealing that they form trimers linked together via disulfide bonds to form hexameric assemblies [8]. Dimerization of RELMβ and resistin was dependent on a cysteine in the N-terminal. This cysteine is lacking in RELMα and RELMγ, suggesting that they may exist as monomers [9,10], however their crystal structure has not been solved. A better understanding of the RELM protein structure may provide important information for identification of the receptors, which remain unknown for many of the RELM proteins.

2.2. Genetic regulation of RELM expression

The genetic regulation and expression profile of the RELM genes have been well characterized from several human and murine studies (Fig. 1**A**). These studies reveal both shared and distinct cellular expression profiles within the RELM gene family (Fig. 1**B**). While some RELM genes, such as RELMα, RELMγ and human resistin, are expressed by hematopoietic cells, mouse resistin, RELMα and RELMβ are expressed in non-hematopoietic cells. All mouse and human RELM proteins are detectable in the serum, offering the potential to utilize RELM levels as biomarkers [11–13]. In this section, we summarize what is known about the cellular expression of RELM genes, the disease settings in which they are expressed, and how they are transcriptionally regulated.

2.2.1. RELMα

RELMα/*Retnla* exhibits the greatest heterogeneity in expression within the RELM family. Under homeostatic conditions, *Retnla* mRNA is present at low levels in the lung, tongue, mammary tissue, and white adipose tissue [6]. Originally discovered as a secreted protein in the bronchio-alveolar lavage of ovalbumin-challenged mice, the consensus from multiple studies using mouse asthma models is that RELMα is highly expressed by airway epithelial cells and type 2 pneumocytes [1,14,15]. Consistent with this, RELMα transcription is driven and critically dependent on a T helper type 2 (Th2) cytokine environment. Indeed, binding sites for the Th2 cytokine-induced transcription factor STAT6 are present within the *Retnla* promoter, and STAT6$^{-/-}$ or IL-

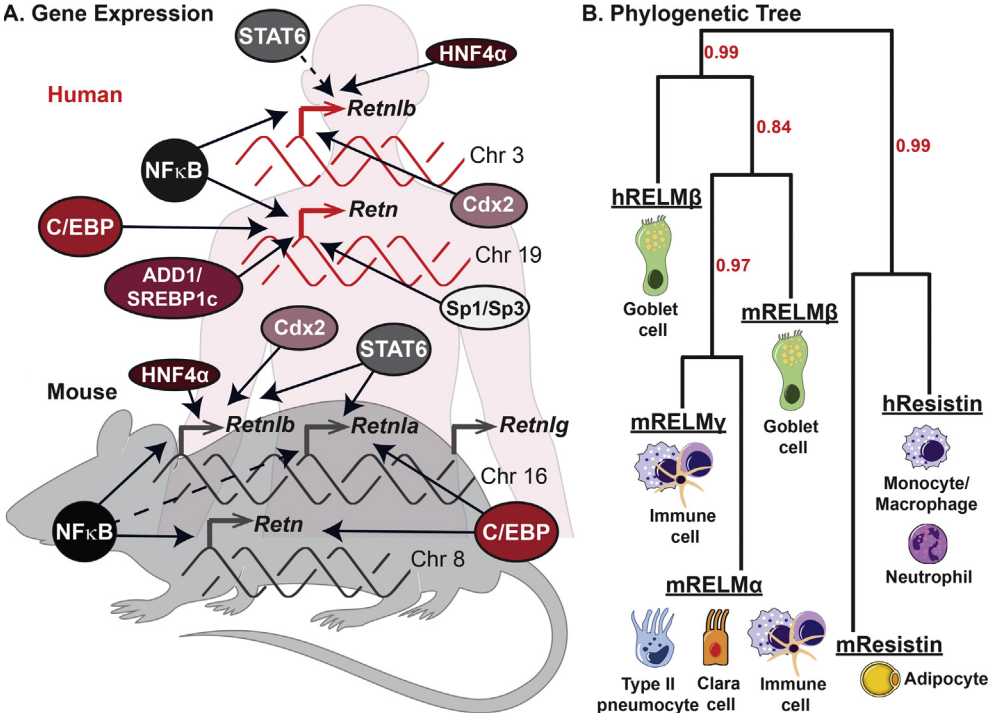

Fig. 1. RELM expression in mouse and man. (A) Genetic regulation and chromosome location of the human and murine RELM genes. Dashed arrows represent putative transcriptional regulation, while solid arrows represent molecularly confirmed transcription factors. (B) Phylogenetic tree illustrating the relatedness of mouse and human RELMs was generated using http://www.phylogeny.fr software. Bootstrap values are indicated in red. The primary cell types that express each RELM are presented.

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