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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-

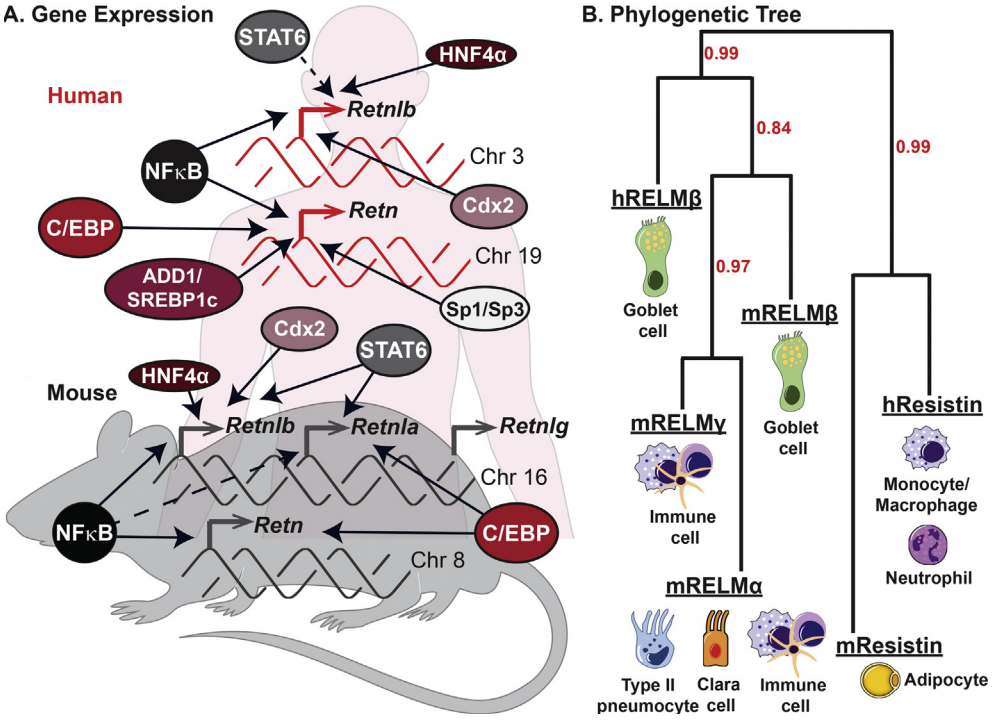

Fig. 1. RELM expression in mouse and man. (A) Genetic regulation and chromosome location of the human and murine RELM genes. Dashed arrows represent putative transcriptional regulation, while solid arrows represent molecularly confirmed transcription factors. (B) Phylogenetic tree illustrating the relatedness 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.

$4^{-/-}$ mice exhibit reduced RELMα expression [16,17]. In addition to expression by non-hematopoeitc cells, RELMα is also recognized as a key signature gene of M2/alternatively activated macrophages that differentiate in chronic, Th2 cytokine-skewed conditions such as helminth or chronic protozoan parasite infection [17–20]. RELMα expression by other immune cells, eosinophils and dendritic cells, has also been reported [18,21]. RELMα is also expressed in lung and peritoneal injury models, and following hypoxic stress [1,22,23]. In these models, RELMα expression may rely on other transcription factors, such as CCAAT/enhancer-binding protein (C/EBP), which binds to its' specific motif adjacent to the STAT6 binding site in the *Retnla* promoter [16]. While RELMα induction can occur in the absence of Th2 cytokine signaling, likely through C/EBP, sustained RELMα expression requires Th2 cytokine stimulation [23]. Interestingly, functional transcription studies revealed that C/EBP binding to the *Retnla* promoter was necessary for IL-4/STAT6-induced *Retnla* expression, suggesting that the STAT6 and C/EBP work in tandem to activate the *Retnla* gene [16]. There are also putative binding sites for Ets family proteins and PPAR, upstream and downstream of the STAT6 binding site respectively [16]. Furthermore, transcription factor binding motifs for NF-κB, GAS, and C/EBP are present throughout the *Retnla* gene, both in the 5′ and 3′ flanking regions and in introns [1].

2.2.2. RELMβ

The RELMβ/*Retnlb* expression pattern in mouse and human studies suggests predominant expression in the secretory granules of intestinal goblet cells, however, expression by lung epithelial cells in asthmatic patients and mouse models of lung fibrosis is also observed [24,25]. Similar to its adjacent gene *Retnla*, the *Retnlb* promoter contains STAT6 binding sites and expression is highly induced by Th2 cytokines *in vivo* in the lung and intestine, and in mouse and intestinal epithelial cell lines [9,26,27]. In addition to regulation by Th2 cytokines, *Retnlb* is also expressed in several intestinal colitis models driven by Th1/Th17 cytokines [28,29]. Additionally, bacterial colonization or lipopolysaccharide (LPS) alone can induce RELMβ expression through the transcription factor Cdx2 [9,30]. Expression in these inflammatory settings is likely through NFκB activation, given the predicted NFκB binding sites within the *Retnlb* promoter. Both the human and mouse *Retnlb* promoters also contain functional binding sites for the hepatocyte nuclear factor 4α (HNF4α), a transcription factor expressed in the liver, kidney, and intestine. Indeed, in a mouse colitis model, overexpression of the HNF4α P2 isoform promoted RELMβ expression and inflammation [31]. In addition to recent studies highlighting the functional significance of HNF4α in intestinal inflammation and cancer, HNF4α is a master regulator of liver function and metabolism [32,33]. Future studies understanding whether RELMβ is a downstream effector of HNF4α may reveal new pathologic pathways in intestinal and metabolic disease.

2.2.3. Resistin

The Resistin/*Retn* gene exhibits an intriguing dichotomy in expression pattern between mouse and man, with expression of mouse *Retn* almost exclusively by murine adipocytes, leading to its alternative name 'ADSF' for adipocyte secreted factor [34]. In contrast, human *Retn* is expressed by immune cells, specifically macrophages, monocytes and neutrophils [13]. The mouse *Retn* gene is considerably larger than the human *Retn* gene and includes a 2279 bp long intron (intron X), with putative transcription factor binding sites: AP1, NF-κB, IRF1, IRF2, HNF3, C/EBP, and a PPAR/RXR heterodimer binding sited called IntX-PPRE [5]. The PPAR/RXR-like protein factors, which are found in differentiated adipocytes, can bind to the PPRE sequence within the mouse *Retn* gene [5]. This suggests that intron X could be responsible for the adipocyte tissue specific expression of *Retn* in mice but not in humans, which lack intron X.

The disparity in introns within the mouse and human *Retn* genes could explain why their expression is regulated differently. For example, TNFα decreased *Retn* expression in mouse adipocytes but increased *Retn* expression human monocytes [35,36]. In contrast, high glucose upregulated both mouse and human *Retn* gene expression, while insulin treatment suppressed *Retn* expression in murine adipocytes and human monocyte cell lines, respectively [35,37]. The high glucose effect was abrogated upon inhibition of MAPKs and NFκB, suggesting their roles in regulating *Retn* expression [37]. Further, similar to the mouse locus, the human *Retn* gene contains adipogenic transcription factor C/EBPα binding sites [38,39]. Additionally, the human *Retn* promoter has a putative binding site for adipocyte determination and differentiation-dependent factor 1 (ADD1)/sterol regulatory element binding protein 1c (SREBP1c) [39]. In mice, binding of C/EBPα to the *Retn* promoter was associated with recruitment of coactivators CREB-binding protein and p300 and abundant acetylation of histones. In this setting, PPARγ ligands were able to inhibit mouse *Retn* expression, likely through inhibition of C/EBPα associated acetylation [38].

Single nucleotide polymorphisms of the human *Retn* gene have been investigated and are correlated with *Retn* gene expression associated with metabolic diseases such as obesity and diabetes. In a Japanese population, SNP −638 G > A and −420C > G resulted in an increase in serum resistin levels [40,41]. This result was partially reproduced in a Korean population that associated SNP −420C > G and the −537A > C with significantly higher plasma resistin levels [42]. At the -420 SNP, stimulatory proteins (Sp) 1 and 3 preferentially bound the −420G over -420C, and could be involved in increasing *Retn* expression under hyperglycemic conditions [43]. Additionally, *Retn* SNP -358 with AG or at least 1 A allele is linked to higher risk of lung cancer than wild-type (GG) carriers in a Chinese Han population [44]. The evidence that polymorphisms may regulate human *Retn* expression is adding to the growing interest in human resistin for its role in immune and metabolic dysregulation. Further analyses on larger and more diverse populations will add to the current knowledge on human resistin expression and function.

2.2.4. RELMγ

RELMγ/*Retnlg* is by far the least studied RELM protein. It is most highly expressed in the hematopoietic system, with high expression in the bone marrow, and lower expression in white blood cells, spleen and thymus [3,7]. While RELMγ is also expressed in the lungs and the adipose tissue, its expression is significantly lower than RELMα [3]. RELMγ has been found to have a proliferative effect on HL60 cells, but did not have an effect on cellular differentiation [7]. The genetic regulation of *Retnlg* expression has not yet been thoroughly examined.

3. RELM putative receptors and downstream signaling

RELMs have been studied and implicated in diverse physiological functions. Surprisingly however, the RELM receptors and downstream signaling pathways are largely elusive. Of the four RELMs, resistin is the only member thus far with a confirmed receptor, whereas the rest of the members are associated with putative or unknown receptors. Fig. 2 summarizes our current understanding of RELM protein signaling and function.

3.1. RELMα

Although extensively studied, the search for a RELMα receptor still continues (Fig. 2**A**). RELMα binding assays revealed that it selectively binds to $CD4^+$ Th2 cells, dendritic cells and macrophages [45]. There is evidence that Bruton's tyrosine kinase (BTK), an important signaling molecule in B cell maturation, is a binding partner for RELMα [45,46] (Fig. 2**A, I**). Immunofluorescent assays have shown that upon RELMα stimulation, BTK redistributes and anchors to the cell membrane where it then co-localizes with RELMα [46]. Given that BTK is an intracellular protein, the exact interaction between the secreted extracellular RELMα

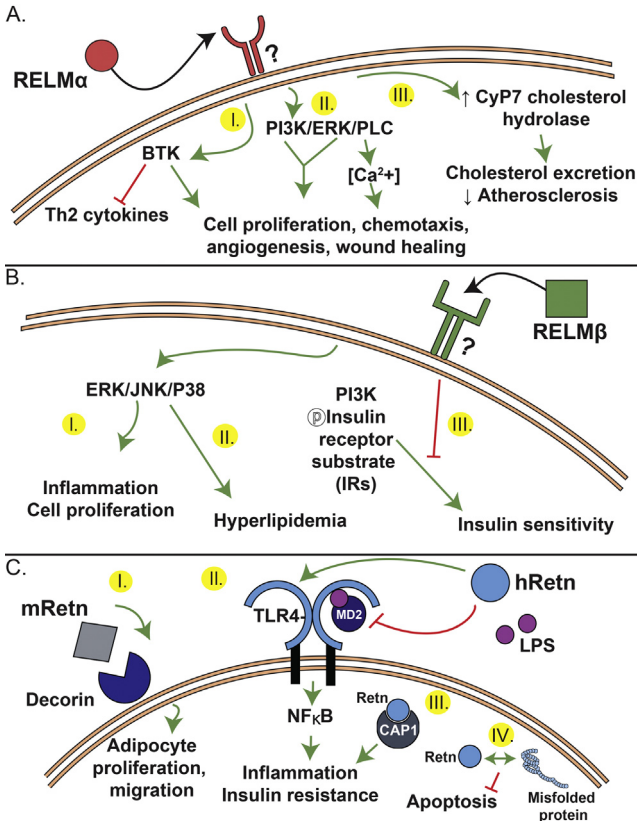

Fig. 2. Proposed receptor and signaling of RELMα (A), RELMβ (B) and Resistin (C).

and intracellular BTK is unclear. Two distinct outcomes of RELMα binding associated with BTK signaling have been reported. First, RELMα induced BTK autophosphorylation and stimulated myeloid cell chemotaxis. Second, in an *in vitro* $CD4^+$ Th2 cell differentiation assay, RELMα downregulated Th2 cytokine production in a BTK-dependent manner [45,46].

Several *in vitro* studies demonstrated a chemotactic and mitogenic function of RELMα, positing a function for RELMα in angiogenesis and tissue remodeling (Fig. 2**A, II**). In human pulmonary artery smooth muscle cells, RELMα increased intracellular Ca^{2+} concentrations by activating inositol 1,4,5-triphosphate receptor (IP_3R) in a phospholipase C dependent mechanism [47]. RELMα also stimulated proliferation of rat pulmonary microvascular smooth muscle cells via the PI3K/AKT signaling pathway, and induced expression of angiogenesis mediators: VEGF and MCP-1, and monocyte recruiting chemokine SDF-1x [1,48]. In a lung fibrosis model, RELMα was implicated in myofibroblast differentiation during lung fibrosis, likely through activation of Notch1 and Jagged1 [49]. While fibroblast activation is detrimental in pulmonary or liver fibrosis, it is a required wound healing process following tissue injury. Recent evidence supports a critical function for RELMα in wound healing through fibroblast activation. Following skin excision wounds in mice, RELMα induced fibroblast expression of lysyl hydrolase 2, an enzyme that mediates collagen cross-linking for skin repair and tissue regeneration [50–52]. Finally, RELMα also acts as an adipokine to regulate metabolic homeostasis [53]. RELMα increased expression of cholesterol-7-α-hydroxylase (Cyp7a1) in hepatocytes by inducing the transcriptional activator liver receptor homologue-1 (LRH-1). This effect was beneficial in hyperlipidemic mice as it promoted excretion of cholesterol in the form of bile acids (Fig. 2**A, III**).

3.2. RELMβ

Similar to RELMα, RELMβ promotes cell proliferation, but has no identified receptor. In human diabetic nephropathy mesangial cells, RELMβ induced phosphorylation of p38MAPK and JNK, and cell proliferation (Fig. 2**B, I**) [54]. In contrast to RELMα, RELMβ contributed to metabolic dysfunction by signaling though MAPK pathways and suppressing insulin signaling in hepatocytes (Fig. 2**B, II-III**). While RELMα binds host cells, murine RELMβ can bind the pore-like structures in the chemosensory apparatus of helminths *Trichuris muris* and *Strongyloides stercoralis*, where it inhibited helminth chemotaxis and feeding [55,56]. Consistent with an anti-microbial function for RELMβ, a recent study showed that both mouse and human RELMβ, and human resistin, could bind gram negative bacteria and permeabilize their membranes [57]. Therefore, while the mechanism of action of RELMα is on the host, RELMβ may act both on the host and the pathogen. It is unclear whether the receptors for these proteins, spanning host and microbe, are similar, however, information from one organism may help guide identification of the receptors in others.

3.3. Resistin

In contrast to RELMα and RELMβ, mouse and human resistin receptors and downstream signaling are better characterized. In adipose stromal cells (ASC), mouse resistin bound to an isoform of decorin (DCN) with functional effects on cell proliferation and migration (Fig. 2**C, I**) [58]. On the other hand, human resistin binds Toll-like Receptor 4 (TLR4), the innate receptor for LPS (Fig. 2**C, II**). Human resistin signaling via TLR4 inhibited LPS binding and function and fatal endotoxic shock in a mouse sepsis model [59,60]. This protective function of resistin can be attributed to a switch from pro-inflammatory (NFκB) to anti-inflammatory signaling pathways (TRIF/TBK-1 and STAT3) [60]. Since TLR4 signaling through Myd88/NFκB is distinct from JAK-STAT3 signaling, human resistin-TLR4 stimulation of STAT3 signaling could be indirect, perhaps through induction of IL-10. While human resistin may be anti-inflammatory in response to a fatal endotoxin challenge, other studies have shown that human resistin alone can promote inflammation [61]. These conflicting findings suggest that the resulting pro-inflammatory or anti-inflammatory function of resistin is context and disease-specific. In colon cancer studies, resistin signaling through TLR4 receptor was described to increase TLR4-MyD88 signaling and SOCS3 expression [62]. The ensuing inhibition of JAK2/STAT3 signaling caused arrest of colon cell growth suggesting that resistin signaling through TLR4 could delay cancer progression [62]. Although LPS is the most recognized ligand for TLR4, human resistin is not the only alternate ligand for TLR4. Indeed, TLR4 is reported to bind saturated fatty acids, the dust mite allergen Derp2, helminth antigens, the host endogenous protein high mobility group box 1 (HMGB) and heat shock proteins [63–68]. Alternate ligands for other TLRs is observed, and suggests that the evolution of TLR signaling and function was likely influenced by both microbial ligand and host endogenous molecules. Whether inflammatory or cancer disease outcomes are altered by these TLR4 alternate ligands in combination or alone is unknown, but needs to be considered when evaluating their overall function.

Adenylyl cyclase-associated protein 1 (CAP1) is also a proposed receptor for human resistin [69] (Fig. 2**C, III**). In monocyte cell lines, resistin-CAP1 interaction led to increased cAMP levels, increased PKA, and NF-κB, and subsequent levels of inflammatory cytokines: IL-6, TNFα, and IL-1β [69]. Intriguingly, CAP1 is an intracellular receptor with no predicted transmembrane domain. Therefore, it is likely that resistin may need to bind a surface receptor, such as TLR-4, for endocytosis and presentation to CAP1. Finally, human resistin has also been described as a molecular chaperone, which binds to misfolded proteins in the cell, protecting it from stress-induced apoptosis (Fig. 2**C, IV**) [70].

Although homologous, RELMs function through various signaling mechanisms that lead to diversified physiological phenotypes. Even though mechanistic studies on RELMs exist, the receptors for these

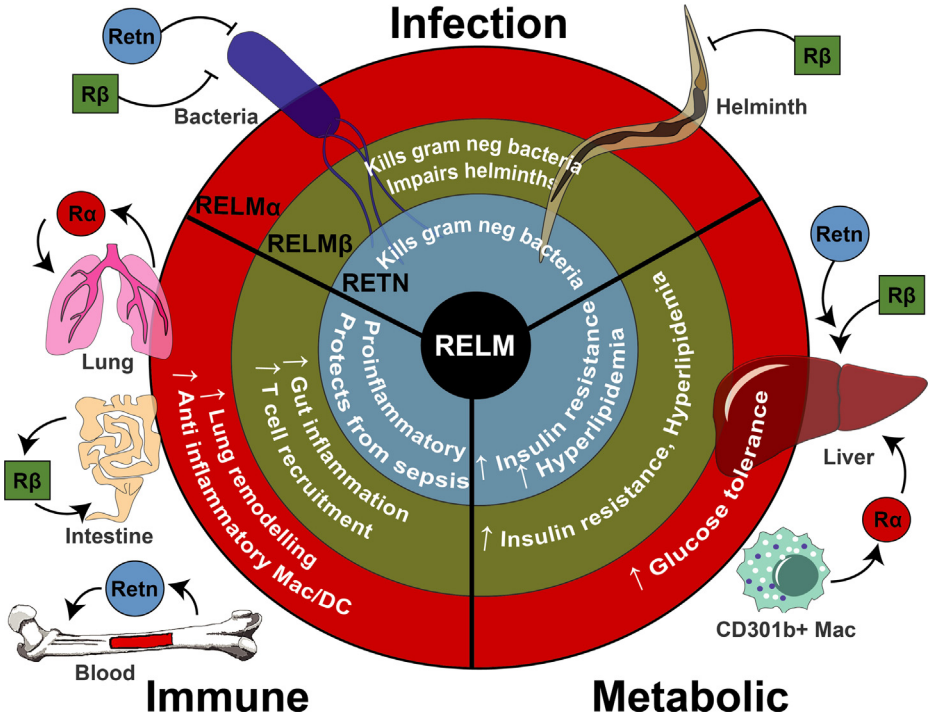

Fig. 3. The diverse roles of RELMs in infection, inflammation and metabolism.

proteins remain elusive. There are also no studies investigating RELMγ signaling. By exploring RELM signaling, it becomes evident that this family of proteins underwent a divergence in their evolution. However, by delving into their physiological functions, we can start to appreciate the similarities that RELMs retained.

4. The long and winding road: RELM function in mice and men

There have been a multitude of diverse studies investigating RELM protein function, some of which reveal opposing functions. This section will review the functional studies on RELMs and their putative roles in infection, inflammatory and autoimmune diseases and metabolic function (summarized in Fig. 3).

4.1. Microbial infection

4.1.1. RELMα

The use of RELMα$^{-/-}$ mice in helminth and bacterial infection as well as helminth antigen sensitization models has revealed complex host immunomodulatory roles for this protein. Following infection with the rat hookworm *Nippostrongylus brasiliensis*, RELMα suppressed Th2 cytokine responses through functional effects on CD4^{+} Th2 cells, which impaired optimal adult worm expulsion [11,45,71]. On the other hand, RELMα's suppression of Th2 inflammation had beneficial effects for the host as it prevented excessive and potentially fatal lung inflammation. It seems therefore that RELMα acts as a critical rheostat in the balance between host immunity and inflammation, preserving host immune homeostasis sometimes at the expense of optimal antimicrobial immunity. In addition to direct suppression of CD4^{+} Th2 cells, RELMα was also able to promote IL-10 producing regulatory T cells following stimulation with *Schistosoma mansoni* antigen-pulsed dendritic cells [21]. In a mouse model of enteropathogenic/enterohemorrhagic bacterial infection with *Citrobacter rodentium*, RELMα-mediated suppression of Th2 cytokines led instead to increased Th17 cytokine-driven inflammation in the colon. Surprisingly, RELMα immunostimulatory effect had no significant effect on bacterial clearance suggesting that RELMα expression in *Citrobacter rodentium* infection was soley detrimental to the host [29,72].

4.1.2. RELMβ

Infection studies with RELMβ$^{-/-}$ mice suggest that RELMβ promotes immunity to helminth and bacterial pathogens. RELMβ$^{-/-}$ mice were more susceptible to *Heligmosomoides polygyrus* and *Nippostrongylus brasiliensis* but not *Trichuris muris* infection [11,55,56,73]. In intestinal bacterial infection with *Citrobacter rodentium*, RELMβ$^{-/-}$ mice succumbed to infection due to mucosal ulceration and deep penetration of the *Citrobacter* into the colonic crypts [74]. Mechanistic studies evaluating RELMβ function suggest that RELMβ's protective effect is twofold: (i) promoting host immune cell responses and (ii) directly killing the pathogen. First, RELMβ promoted CD4^{+} T cell recruitment to the *Citrobacter*-infected intestines and increased production of antimicrobial cytokine IL-22 [74]. Additionally, recombinant RELMβ treatment of macrophage and splenocyte cultures promoted Th1 immune responses, which are protective in bacterial and viral infections, but not in chronic helminth infection [73]. Second, RELMβ binds both helminths and gram negative bacteria, leading to impaired helminth function and bacterial killing, respectively [55–57]. This microbicidal role for RELMβ is also shared by murine and human resistin.

Although not explored in the context of infection, there is strong evidence that RELMβ shapes the host microbiome. Compared to conventionally housed mice, germfree mice exhibited deficiency in intestinal RELMβ expression in the intestine that was restored upon colonization with commensal bacteria [9]. This effect was not entirely recapitulated with LPS treatment, suggesting that other bacterial factors regulate RELMβ expression [9]. However, when intestinal cell lines were directly stimulated with LPS, there was only a modest expression of RELMβ [9]. Between these two observations, it is likely that the microbiome within the colon can induce the expression of RELMβ, however, this expression was not purely driven by LPS expression and there are likely other bacterial factors in play. Recombinant RELMβ has antibacterial activity against gram negative bacteria, by binding to negatively charged lipids and creating multimeric pores within the membrane [57]. Because of this antimicrobial activity, RELMβ likely prunes the microbial communities present within the colon. Indeed,

microbiome evaluation of wild-type and RELMβ$^{-/-}$ mice revealed increased gram negative bacterial invasion into the colon inner mucus layer, and increased abundance of Proteobacteria including *Helicobacter* [57]. Whether RELMβ's functional effects on the bacterial and helminth infection are in part mediated by its influence on the microbiome remains to be determined.

4.1.3. Resistin

Human resistin function has been explored in helminth and viral infections. In both chronic filarial nematode infection and intestinal ascaris infection, plasma resistin levels were elevated and correlated with increased parasite burden and increased inflammatory cytokines TNFα, CCL2 and IL-6 [13]. The findings in these correlative studies were validated *in vivo* by employing human resistin transgenic mice [13]. Here human resistin expression led to increased *Nippostrongylus brasiliensis* parasite burdens, correlated with increased TNFα and CCL2 gene expression. The effect of resistin in promoting a susceptible phenotype to helminth infection is similar to RELMα, however, instead of inhibiting Th2 cytokines, it seems that resistin tips the balance from a Th2-type response to a proinflammatory cytokine response. Again, similar to RELMα, it seems the role of resistin in helminth-infected hosts is counterintuitive. However, it is likely that resistin exists to direct the immune response towards combating more fatal bacterial or viral infections in an environment where bacterial-worm co-infections are common. Consistent with this, resistin has microbicidal properties and could protect mice from fatal endotoxic shock [57,60]. Interestingly, compared to human resistin, mouse resistin did not have an impact on parasite burdens [13]. An explanation for this could be that human and mouse resistin expression are regulated differently and therefore have divergent functions in helminth infection. Mouse resistin and its role in helminth infection, if any, has yet to be uncovered.

Patients with chronic Hepatitis B viral infection had significantly elevated serum resistin levels, that were increased with progression to HBV-associated liver cirrhosis and liver failure [75]. In chronic Hepatitis C virus-infected patients, a correlation exists between resistin and liver fibrosis severity [76]. In patients with HCV-induced chronic hepatitis, resistin expression was found to be higher in areas with inflammation and ongoing fibrogenisis [77]. Whether resistin is an instigator of viral-induced inflammation or is simply a result of viral infection is yet unclear.

4.2. Inflammatory and fibrotic disease

As in infection, the role for RELM proteins in influencing the immune response is recognized in several studies on inflammatory and fibrotic diseases. However, whether they play a pathogenic function in stimulating inflammation, or instead protect against excessive inflammatory responses is controversial. Some of this conflicting evidence may be caused by discrepancies between correlative and functional studies, while another contributor may be the use of endotoxin-contaminated bacterially-derived recombinant proteins. In addition to these caveats, it is becoming increasingly clear that the disease context and RELM protein level and expression pattern may be critical for their beneficial or pathologic outcomes.

4.2.1. RELMα and RELMβ

RELMα is highly expressed in lung injury and allergic airway inflammation models, where several studies, using recombinant RELMα administration or RELMα-expressing transgenic mice, confirmed a function in promoting chemotaxis for eosinophils and dendritic cells, and vascular inflammation [48,78–80]. On the other hand, RELMα$^{-/-}$ mice exhibited similar airway and lung inflammation compared to wild-type mice following ovalbumin or *Aspergillus*-induced allergic airway inflammation [81]. In another study using RELMα-overexpressing transgenic mice, RELMα significantly suppressed ovalbumin-induced Th2 lung immune responses, correlated with reduced pERK signaling [14]. This is consistent with the original studies reporting RELMα$^{-/-}$ mice, where RELMα dampened the Th2 lung inflammatory response to sensitization and challenge with helminth *Schistosoma mansoni* egg antigen [45,71].

In several studies investigating dextran sodium sulfate-induced intestinal inflammation as a mouse model of ulcerative colitis, RELMα$^{-/-}$ and RELMβ$^{-/-}$ mice exhibited reduced intestinal pathology and Th17 and TNFα cytokine responses compared to wild-type mice [29,31,82,83]. In contrast, RELMβ$^{-/-}$ mice suffered from more severe trinitrobenzene sulfonate-induced colitis, as a model for Crohn's disease, compared to wild-type mice [83]. The functional consequence of human RELMβ in IBD patients has yet to be determined, however, the mouse studies suggest that RELMβ's role may be different depending on the type of inflammatory bowel disease (ulcerative colitis versus Crohn's disease).

RELMα function in tissue repair and fibrosis is better understood with several studies showing that RELMα promotes these processes. Both tissue repair and fibrosis share similar pathways, such as stimulation by Th2 cytokines [84]. However, tissue repair is the desired outcome to injury while fibrosis, or scarring, occurs when tissue repair is not kept in check. Given that RELMα is stimulated by Th2 cytokines following both lung and skin injury, it was posited that RELMα maybe the downstream mediator of Th2 cytokine-induced tissue repair. Supportive of this, RELMα promoted myofibroblast differentiation and increased expression of type 1 collagen and α-SMA expression, leading to thickened fibrotic dermis and extracellular matrix deposition in bleomycin-induced dermal fibrosis [85]. Another study using skin biopsy-induced injury showed that IL-4 activated RELMα mediated skin healing by controlling collagen fibril assemby [50]. RELMα was profibrotic in bleomycin-induced pulmonary fibrosis through several proposed mechanisms: bone marrow cell recruitment, increased expression of VEGF, fibroblast and myofibroblast activation [86,87]. Similar to RELMα, murine RELMβ also promoted bleomycin-induced pulmonary fibrosis, associated with increased lung fibroblast proliferation, collagen expression, and leukocyte recruitment [88]. Of clinical significance, human asthmatic patients have RELMβ deposits in the extracellular matrix associated with increased airway remodeling [24].

4.2.2. Resistin

Increased circulating levels of resistin are observed in several human inflammatory diseases including endotoxemia, sepsis, rheumatoid arthritis and inflammatory bowel disease [89]. *In vitro* human monocyte culture and *in vivo* studies with human resistin-expressing transgenic mice suggest that resistin is a stimulatory cytokine that promotes immune cell activation and chemotaxis, neutrophil extracellular trap formation and inflammatory cytokine production [61,69]. More recent studies reveal that resistin may be anti-inflammatory in certain contexts. Resistin could impair LPS function and protect against high dose LPS-induced endotoxic shock [60]. Intriguingly, serum resistin levels were lower in patients with myalgic encephalitis/chronic fatigue syndrome, and was associated with reduced disease severity in patients with moderate to severe disease [90]. More functional studies are needed to determine the contribution of resistin to these immune-mediated diseases.

4.3. Cancer

While there are no reports on RELMα expression or function in cancer, human RELMβ expression was detected in 65.4% of 136 human cases of gastric cancers, where there was a positive correlation between RELMβ expression and patient survival [91]. Additionally, murine RELMβ was associated with reduced susceptibility to azoxymethane and DSS induced colorectal cancer, indicating that RELMβ could have a protective role in cancer [92]. Mechanistically, RELMβ decreased Th2 cytokine levels, it was suggested that RELMβ may indirectly slow the progression of colon cancer by decreasing inflammation [92]. In

contrast, another study found that RELMβ overexpression in gastric carcinoma cells significantly increased invasion and migration of gastric cancer cells in a transwell assay [93]. Thus, RELMβ expression in gastric cancer may have a more complicated mechanism than initially predicted.

Resistin is reported to have indirect effects within inflammatory cancers. As previously mentioned, resistin signaling through TLR4-ERK-SOCS3 delays the progression of colonic cancers [62]. However, the arrest in cell cycle led to these cancer cells being more resistant to chemotherapeutic drugs that target highly proliferating cells. Further, another study showed that resistin blocked the apoptotic effect of the chemotherapy drugs, bortezomib or carfilzomib [94]. Here, treatment of various cancer cell lines with resistin resulted in upregulation of the transporter genes *ABCC5*, and *ABCG2*, that could act to export the drugs outside the cells [94]. In conclusion, it seems that both RELMβ and resistin are protective in inhibiting cancer progression, but may interfere with chemotherapy.

4.4. Metabolic function

4.4.1. RELMα and RELMβ

RELMα expression is observed within white adipose tissue of high fat diet-fed mice [53]. RELMα deficiency in hyperlipidemic and atherosclerotic mice resulted in significant cholesterol increase, while overexpression of RELMα resulted in the reverse effect [53]. Mechanistically, RELMα overexpression upregulated the liver cholesterol catabolic enzymes, Cyp7a1 and Cyp8b1, which are responsible for breaking down cholesterol and converting it to bile acid. Consistent with this, RELMα overexpressing mice had increased fecal bile acid content and fecal cholesterol indicating a RELMα-mediated mechanism for cholesterol breakdown and clearance. RELMα thus induces depletion and clearance of cholesterol, and further implies that RELMα has beneficial functions in metabolism. However, in another study, RELMα expressed by CD301b$^+$ mononuclear phagocytes within the white adipose tissue was important in maintaining healthy body weight and glucose levels [95]. When CD301b$^+$ mononuclear phagocytes were depleted, there was a significant downregulation of metabolic genes in the liver, associated with hyperglycemia. This effect was reversed when the mice were exogenously treated with recombinant RELMα. In contrast, another study reported that RELMα$^{-/-}$ mice were protected from hyperglycemia [96]. It is possible that these discrepancies reflect differences in cell-specific deletion of CD301b$^+$ cells compared to whole body RELMα$^{-/-}$ mice.

It is now well recognized that the immune environment, particularly the Th1/Th2 cytokine balance, is an important contributor to metabolic homeostasis or disease [97]. Given that RELMα is expressed by M2 macrophages, and regulates Th2 cytokines, it is possible that RELMα's effect in metabolism is partly mediated through its immunoregulatory function. For example, brown adipose tissue in lean mice is more heavily populated with cells such as M2 Macs and Tregs as well as IL-4, IL-13 and IL-10 cytokines resulting in an overall Th2 immune state that maintains a noninflammatory mileu [98]. In contrast, chronically inflamed white adipose tissue associated with obesity and insulin resistance is populated with effector M1 macrophages that primarily contribute to a proinflammatory IL-1β, TNF-α and IL-6-rich environment [98]. In contrast to RELMα, however, resistin is associated with proinflammatory macrophage activation in obesity, but recent studies suggest that resistin can be anti-inflammatory in certain disease contexts [60]. More specific studies investigating the immune effects of the specific RELM proteins in obesity and diabetes are necessary, however, the current data may support a therapeutic benefit in employing RELM proteins to modulate the Th1/Th2 balance to treat metabolic dysfunction.

RELMβ is highly expressed in mice fed a high fat diet [99] and RELMβ$^{-/-}$ mice exhibited reduced glucose tolerance [92]. In contrast, transgenic mice overexpressing RELMβ in hepatocytes suffered from increased hyperglycemia, hyperlipidemia, fatty liver, and pancreatic islet enlargement when fed a high fat diet [100]. Further, recombinant RELMβ treatment suppressed insulin signaling in cultured hepatocytes, associated with increased MAPK and reduced IRS1/2 proteins [100]. These studies suggest that, similar to RELMα, RELMβ's effect on glucose tolerance and insulin signaling is dependent on the *in vivo* context and RELMβ level. Indeed, high RELMβ levels in the liver cause metabolic dysfunction, however, complete abrogation of RELMβ expression is also detrimental.

4.4.2. Resistin

Resistin's function in metabolism has been explored thoroughly, and is discussed in a number of recent review articles [89,101,102]. The general consensus in mouse and human studies is that resistin plays a pathologic role in promoting insulin resistance, atherosclerosis and hypertension. Here we will focus on a few select studies investigating resistin in metabolic disease. In mice, inhibition or genetic deletion of resistin resulted in increased insulin sensitivity and glucose homeostasis [103]. Conversely administration of exogenous resistin, or transgenic expression of human resistin, promoted insulin resistance [103–106]. Some population studies have reported an association between circulating resistin levels and adiposity or increased insulin resistance [41], but other studies have challenged this link [107–109]. A bigger dataset, and more focused analysis parameters or exclusion criteria to reduce confounding factors, may address human resistin's metabolic function. Both human and mouse resistin reduced insulin-induced glucose uptake within cardiomyocyte cells, most likely by impairing insulin-mediated GLUT4 translocation [110]. Further, in patients with coronary artery disease, elevated resistin levels were correlated with aortic stiffness [111]. It was hypothesized that resistin's induction of insulin resistance changes glucose metabolism, which causes stress to the heart when it shifts to glucose as its energy source, and leads to heart failure. If this theory is confirmed, resistin management may prove to be a viable option for preventive treatment in patients with cardiac disorders. Given that resistin is an immunomodulatory molecule secreted by immune cells, resistin's cross-talk with the immune system is a likely contributor to its' metabolic effect.

5. Concluding remarks and perspective

Whether resistin and the RELM proteins are helpful or detrimental for the host is still under debate, however, this review has highlighted the complexity in interaction and function of these proteins, which suggests that their role cannot purely be defined as "positive" or "negative". For example, RELMα's chemotactic and proliferative properties may lead to inflammation but is beneficial in wound healing, which requires immune contribution. Further, RELM proteins may have therapeutic potential. For instance, RELMα and resistin's ability to attenuate excessive inflammatory responses may be valuable in clinical settings. Conversely, RELMβ and resistin's microbicidal properties could be harnessed as new antimicrobial agents against bacteria and helminths. Likewise, RELMβ's inhibitory effect on cancer cell proliferation and its association with improved survival could be investigated as a potential biomarker or therapy. Last, RELMα's beneficial effect in metabolic homeostasis could be explored to target metabolic disease.

While we have attempted to comprehensively address key studies investigating RELM protein expression and function at both the molecular and whole body level, we also highlight missing or conflicting information. First, research on the receptors and activation mechanisms for these proteins is incomplete. Second, given that RELM proteins seemingly influence metabolic, immune and microbial systems, more multidisciplinary research to understand how effects in one system may have outcomes in another system may shed light on the conflicting information in the field. It is also possible that the effects of RELM proteins are more nuanced, and overexpression or whole body

knockout data represent extremes in the spectrum of RELM function. Instead, experiments investigating varied concentrations or cell-specific expression of these proteins could be useful to examine their potential as biomarkers or therapeutics. While we have come a long way in research of resistin and resistin-like molecules, there is still much work to do.

Authors contributions

GP and MGN: Concept and design, drafting of the manuscript
HMB: Drafting of the manuscript, figure design

Competing interests

The authors have no competing interests to declare.

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