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Resolving inflammation by TAM receptor activation

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ABSTRACT

The control of inflammation is strictly regulated to ensure the adequate intensity and duration of an inflammatory response, enabling the removal of the trigger factors and the restoration of the integrity of the tissues and their functions. This process is coordinated by anti-inflammatory and pro-resolving mediators that regulate the cellular and molecular events necessary to restore homeostasis, and defects in this control are associated with the development of chronic and autoimmune diseases. The *TAM family* of *receptor* tyrosine kinases—Tyro3, Axl, and MerTK—plays an essential role in efferocytosis, a key process for the resolution of inflammation. However, new studies have demonstrated that TAM receptor activation not only reduces the synthesis of pro-inflammatory mediators by different cell types in response to some stimuli but also stimulates the production of anti-inflammatory and pro-resolving molecules that control the inflammation. This review provides a comprehensive view of TAM receptor family members as important players in controlling inflammatory responses through anti-inflammatory and pro-resolving actions.

Contents

1. Introduction

Inflammation is an essential host defense response in vascularized tissue injury caused by a harmful stimulus. It is considered a physiological process for removing trigger insults and cell debris, enabling the maintenance of tissue homeostasis (Medzhitov, 2008, 2010). During the inflammatory process, important cardinal macroscopic and physiological signs are revealed, including redness, swelling, increased local or systemic temperature, and pain. These events are commonly seen in acute inflammation and are underlined by microscopic phenomena, as the release of soluble inflammatory mediators, causing vascular alterations and leukocyte recruitment to the affected tissue (Medzhitov, 2010; Nathan, 2002). In the initial phase of inflammation, harmful agents are sensed by innate immune receptors in tissue-resident cells, leading to cell activation and the production of a plethora of pro-inflammatory mediators belonging to different classes of molecules, such as eicosanoids, vasoactive amines, cytokines, and chemokines (Medzhitov, 2010). Vascular endothelial cells early recognize these factors, increasing their permeability with consequent exudation of plasma

Abbreviations: BMDMs, Bone-marrow derived macrophages; Gas6, Growth Arrest-Specific 6; IL, Interleukin; LPS, Lipopolysaccharide; M1, Classically activated macrophages; M2, Alternatively activated macrophages; Mres, Resolving macrophages; Pros1, Protein S; SPMs, Specialized pro-resolving mediators; TAM, —Tyro3, Axl, and MerTK—receptors.

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proteins and fluid from the blood into the tissue. In addition, the increased tissue blood supply and the upregulation of vascular adhesion molecules and chemoattractant factors potentiate leukocyte migration from the circulation to inflammatory site (Mantovani, Cassatella, Costantini, & Jaillon, 2011; Medzhitov, 2010; Nathan, 2002). Such rapid leukocyte recruitment and accumulation (granulocytes at first) into the injured tissue have a pivotal function in promoting the elimination of injurious stimuli (Mantovani et al., 2011). However, despite combating the inciting agent, excessive and uncontrolled granulocyte influx can be noxious and potentiate damage to adjacent tissues (Nathan, 2002; Nathan & Ding, 2010; Serhan et al., 2007). Thus, the fine-tuned regulation of tissue inflammation is critical for a self-limited response and its proper resolution, but variables such as the intensity of inflammation and the persistence of stimuli might impair the balance of pro-inflammatory, anti-inflammatory, and pro-resolving molecules in the course of an inflammatory response (Serhan & Savill, 2005; Sugimoto, Sousa, Pinho, Perretti, & Teixeira, 2016). In this context, TAM receptor family members have been shown to play important anti-inflammatory and pro-resolving functions in different contexts of inflammation, making them key regulators of inflammatory diseases.

2. Molecular structure of TAM family members and their involvement in inflammatory diseases

TAM (Tyro3, Axl, and MerTK) receptor tyrosine kinases (RTKs) and their cognate glycoprotein ligands growth arrest-specific 6 (Gas6) and protein S (Pros1) are critical regulators of tissue homeostasis and inflammation. These molecules are expressed by a broad range of cells that participate in many physiological events, including coagulation cascade, neuron survival, fertility, and immune system activation (Rothlin, Carrera-Silva, Bosurgi, & Ghosh, 2015). All three TAM receptors share similar structures in both extracellular (amino-terminal) and intracellular (carboxyl-terminal) domains. The amino-terminal domain is composed of two immunoglobulin-related domains (which mediate ligand binding) and two fibronectin type III (FNIII) repeats, while the tyrosine kinase domain (carboxyl-terminal) that is responsible for downstream cytoplasmic signaling after TAM activation is localized intracellularly (Fig. 1A) (Lemke, 2013). TAM ligands Gas6 and Pros1 share ~42% sequence homology and are constitutively γ-carboxylated on glutamic acid residues (Gla domain) of their amino-terminal structure (Fig. 1A, B), a vitamin K-dependent process (van der Meer, van der Poll, & van ' t Veer, 2014). The carboxylation of the Gla domain is an important process for Ca^{+2} binding, which favors the interaction with anionic molecules, such as phosphatidylserine, present in apoptotic cells, tumor cells, and enveloped virus (Lew et al., 2014; Tsou et al., 2014).

Gas6 and Pros1 bind to TAM through the laminin G (LG) domains of their carboxyl-terminal sex hormone-binding globulin (SHBG) domain (Fig. 1A). While Gas6 can bind to all three TAM receptors with higher affinity to Axl, Pros1 can activate Tyro3 (higher affinity) and MerTK, but not Axl (Fig. 1B) (Lew et al., 2014; Tsou et al., 2014). The post-translational modification of Gas6 and the Pros1 Gla domain (γ-carboxylation) favors their association with phosphatidylserine and optimizes their interaction with TAM receptors (Lew et al., 2014). The efficient bridge between Gas6- or Pros1-oponized apoptotic cells and phagocytes promotes the engulfment of apoptotic cells, a phenomenon called efferocytosis, a crucial step for the resolution of inflammation (Lew et al., 2014; Morizono & Chen, 2014). A post-translational modification of TAM occurs through the action of metalloproteinases, particularly ADAM17, shedding their ectodomain structures generating soluble forms of these receptors (Fig. 1C) (O'Bryan, Fridell, Koski, Varnum, & Liu, 1995; Thorp et al., 2011). All three TAM receptors can be found in their soluble forms in inflammatory environments, which make important contributions to the modulation of inflammatory responses as scavenger receptors for TAM ligands. However, while sTyro3 and sAxl are still able to bind to TAM ligands, albeit with reduced affinity compared to membrane forms, sMerTK loses its affinity to the ligands, not acting as decoy receptor (Fig. 1C) (Tsou et al., 2014).

Increased detection of local or systemic sTAM in fluids is generally associated with disease severity, either scavenging TAM ligands, or a reduced availability of membrane-form receptors. For instance, high plasma levels of sMerTK and sAxl have been demonstrated in patients with systemic lupus erythematosus (SLE), with positive correlation with the disease activity, inflammatory processes and nephritis (Ekman, Jonsen, Sturfelt, Bengtsson, & Dahlback, 2011; Wu et al., 2011). Similar findings have also been demonstrated with serum sMerTK in patients with Sjögren's syndrome (Qin et al., 2015) and with serum or synovial fluid sTyro3 in rheumatoid arthritis (Vullings et al., 2020; Xu et al., 2018), which is directly related to the severity of the diseases. In the next sections, we provide detailed information about the molecular actions of TAM family members to control inflammatory responses, demonstrating their anti-inflammatory and pro-resolving properties.

3. Common and distinctive features of anti-inflammation and resolution of inflammation

Anti-inflammatory and pro-resolving mechanisms are complementary and well-coordinated events involved in the control and end of tissue inflammation. Conceptually, anti-inflammation is related to the reduction or elimination action of pro-inflammatory mediators, and this is achieved by limiting their synthesis, blocking their action either by selective antagonists or by extracellular scavenger molecules, or through their enzymatic post-translational modification or degradation (Serhan et al., 2007). Therapeutically, anti-inflammatory compounds have been extensively and successfully used for centuries, and continuous advances have been made to develop innovative agents, improving their pharmacology, reducing side effects, and discovering new targets. The list of anti-inflammatory compounds is extensive, ranging from endogenous/natural (cortisol and plant-derived molecules (*e.g.*, flavonoids)) to synthetic and neutralizing antibody-based molecules (glucocorticoids, receptor antagonists, and anti-cytokine monoclonal antibodies). Although the short-term use of anti-inflammatory medicines is relatively safe, their prolonged use, as in chronic inflammatory diseases, is commonly accompanied by notable side effects in a particular organ (*e.g.*, reduced mineral density and an increased risk of fracture in bone; metabolic effects, such as impaired glucose metabolism and insulin resistance; gastrointestinal effects, such as bleeding and stomach aches; and dermatological issues, including skin atrophy and disturbed wound healing) and an increased risk of immunosuppression (Patrignani, Tacconelli, Bruno, Sostres, & Lanas, 2011; van der Goes, Jacobs, & Bijlsma, 2014).

Different to anti-inflammation, the resolution of inflammation is a tightly controlled and active process that potentiates the elimination of inciting stimuli, promoting the apoptosis and efferocytosis of polymorphonuclear (PMN) cells, stimulating the non-phlogistic recruitment of macrophages, and macrophage reprogramming (Serhan et al., 2007; Serhan & Savill, 2005; Sugimoto, Vago, Perretti, & Teixeira, 2019). These events favor the end of inflammation and the restoration of tissue homeostasis. The key mechanisms of resolution of inflammation are summarized in Fig. 2.

The knowledge of pro-resolving mechanisms has been acquired mainly through acute self-resolving inflammatory models, where the complete resolution is simplified by the analysis of total clearance of PMN accumulation in the inflammatory site, with the resolution phase expanding from the peak of PMN accumulation to their complete decline in the affected tissue. Although conceptually simplistic, these systems are effective, allowing for the identification of key endogenous pro-resolving molecules and their correlation along the different phases of inflammation, as well their main sources (Serhan et al., 2007). Importantly, pro-resolving molecules may also present anti-inflammatory effects, for example blocking pro-inflammatory signals and PMN

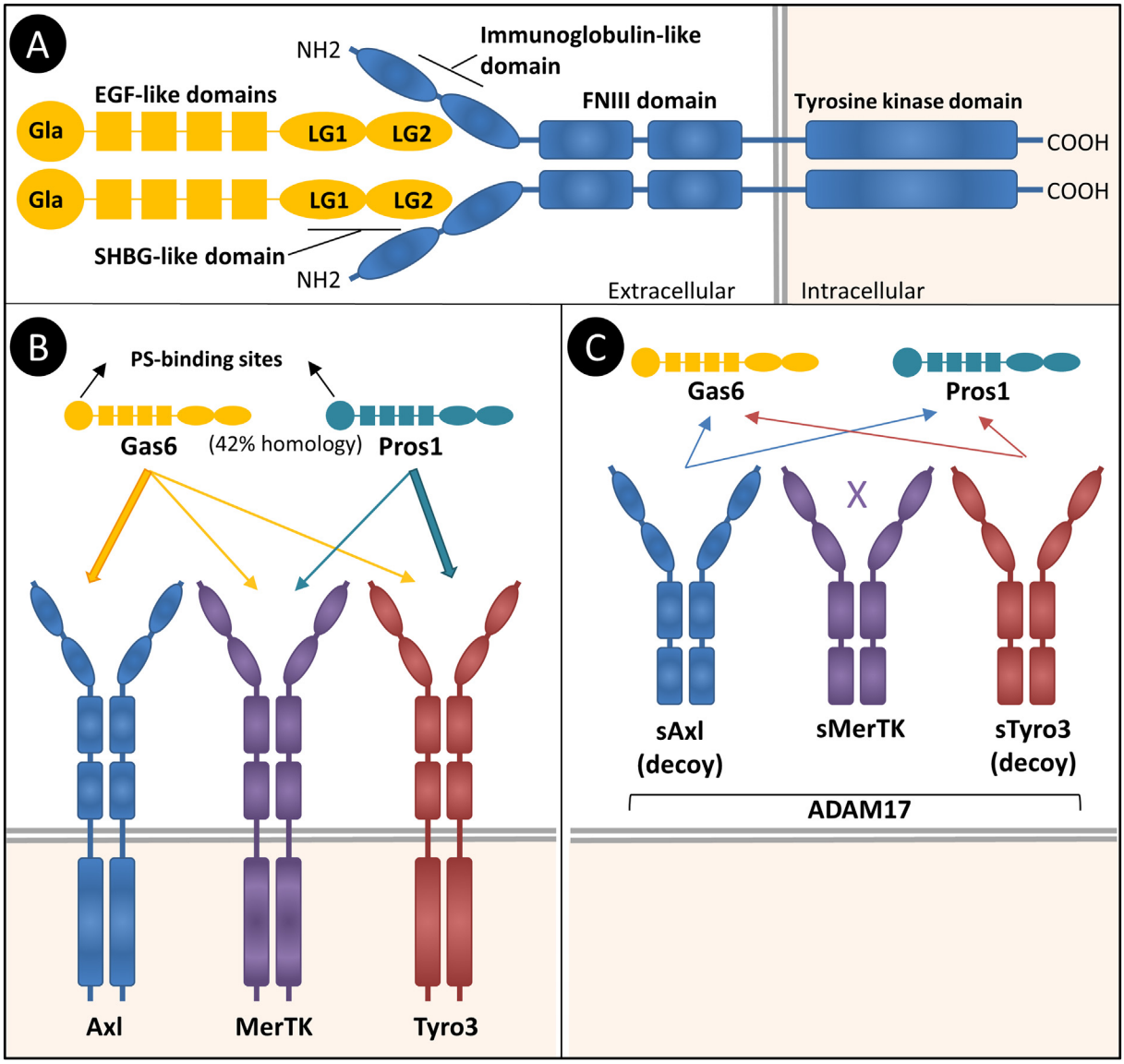

Fig. 1. Representative scheme of TAM receptors' structures and interactions with their ligands. TAM receptors, represented in dimers in the picture, share a similar structure composed of two immunoglobulin-like domains (extracellular), two FNIII domains (extracellular) and a tyrosine kinase domain (intracellular). TAM ligands Gas6 and Pros1 have a Gla domain, four EGF-like domains, and two LG domains (SHBG-like domain) **(A)**. TAM receptors show complex interaction with their ligands Gas6 and Pros1. Binding analysis shows that Gas6 binds to all three receptors, while Pros1 binds to MerTK and Tyro3, but not to Axl. The intensity of interaction between the ligands to each receptor is represented by the thickness of the arrows **(B)**. The release of the ectodomain structures of TAM receptors by ADAM17 generates their soluble forms, which can work as decoy receptors, except sMerTK **(C)**. Abbreviations: EGF, epidermal growth factor; FNIII,fibronectin type III; Gla, γ-carboxyglutamic acid; LG, laminin G; PS, phosphatidylserine; SHBG, sex hormone-binding globulin.

recruitment. However, anti-inflammatory molecules do not necessarily exhibit pro-resolving properties, for example, inducing macrophage reprogramming and enhancing efferocytosis. In addition, it has already been described that early anti-inflammatory therapy, administrated during the initial steps of inflammation, can affect the production of pro-resolving mediators, especially those derived from polyunsaturated fatty acids (specialized pro-resolving mediators, SPMs) (Fukunaga, Kohli, Bonnans, Fredenburgh, & Levy, 2005). Since polyunsaturated fatty acids (for example, arachidonic acid and eicosapentaenoic acid) are precursors for both pro-inflammatory mediators (prostaglandins and leukotrienes) and specialized pro-resolving mediators (SPMs) (Levy, Clish, Schmidt, Gronert, & Serhan, 2001), blocking inflammation at early stages can also be detrimental to resolution. The best known pro-resolving molecules and their precursors are listed in Table 1.

During the elimination of the harmful agents in the initial phase of inflammation, reduction in the synthesis and an increase in the catabolism of pro-inflammatory mediators take place in the affected tissue. On the other hand, the production and release of anti-inflammatory and pro-resolving mediators increase, providing the basis for the subsequent events of the resolution of inflammation (Serhan & Savill, 2005; Sugimoto, Sousa, et al., 2016). Both processes occurs in a balancing way, contributing to the prevention of the further migration of granulocytes and even increasing their apoptosis through the restriction of survival factors (Serhan et al., 2007). In fact, a key feature of the resolution of acute inflammation is the recognition and phagocytosis of apoptotic granulocytes by macrophages (Duffin, Leitch, Fox, Haslett, & Rossi, 2010; Savill et al., 1989). In this context, there is an essential recruitment of non-phlogistic macrophages during the resolving phase of inflammation, amplifying the clearance of apoptotic granulocytes (McArthur et al., 2015). Effective efferocytosis reprograms macrophages from a pro-inflammatory to an anti-inflammatory phenotype (Ariel & Serhan, 2012). Macrophages display significant plasticity that can be referenced to Th1/Th2 polarization. In brief, two distinct states of activation for macrophages have been suggested: “classically activated”,

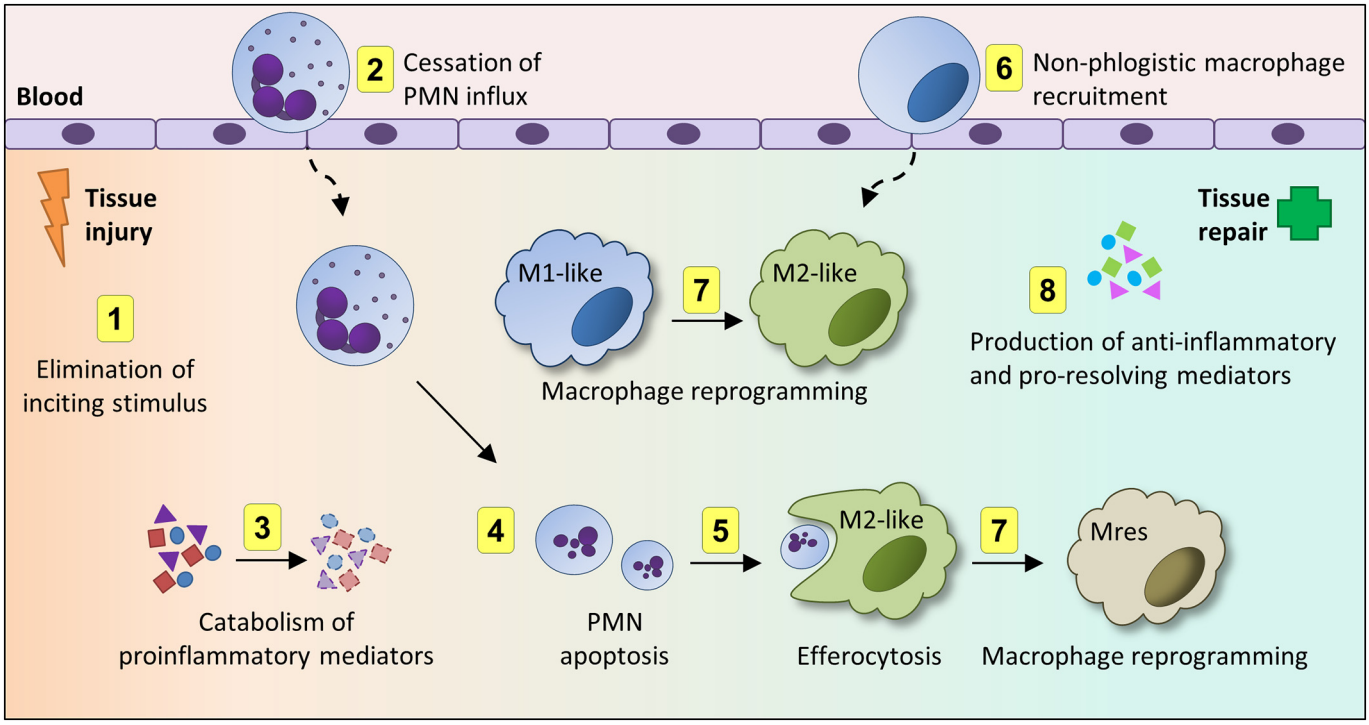

Fig. 2. Key steps for proper resolution of inflammation. The resolution of inflammation is an active and orchestrated process, which involves activation of several mediators and cellular events to ensure rapid and successful restoration of tissue homeostasis. An overview of the essential events for proper resolution of inflammation is shown in **1–8**.

known as M1 macrophages, and "alternatively activated", established as M2 macrophages (Ariel & Serhan, 2012; Lichtnekert, Kawakami, Parks, & Duffield, 2013; Mantovani, Biswas, Galdiero, Sica, & Locati, 2013).

During the onset of inflammation, M1-polarized macrophages are involved in the production of pro-inflammatory cytokines, reactive oxygen species (ROS), nitric oxide (NO) and phagocytosis, important tools

Table 1
The best known pro-resolving molecules and their precursors.

	Mediator	Class	Precursor	Reference
SPMs	Lipoxins: LXA_4, LXB_4, 15-epi-LXA_4, 15-epi-LXB_4	Lipid	Arachidonic acid	(Chiang & Serhan, 2017)*
	Resolvins D series: RvD1, RvD2, RvD3, RvD4, RvD5, RvD6	Lipid	Docosahexaenoic acid	(Chiang & Serhan, 2017)*
	Resolvins E series: RvE1, RvE2, RvE3	Lipid	Eicosapentaenoic acid	(Chiang & Serhan, 2017)*
	Protectins: PD1, 17-epi-PD1	Lipid	Docosahexaenoic acid	(Chiang & Serhan, 2017)*
	Maresin-1	Lipid	Docosahexaenoic acid	(Serhan, Chiang, & Dalli, 2018; Tang, Wan, Huang, Stanton, & Xu, 2018)*
	MCTRs	Lipid	Docosahexaenoic acid	(Serhan et al., 2018; Tang et al., 2018)*
	PCTRs	Lipid	Docosahexaenoic acid	(Serhan et al., 2018)*
	RCTRs	Lipid	Docosahexaenoic acid	(Serhan et al., 2018)*
Others	α-MSH	Peptide	Proopiomelanocortin	(Montero-Melendez, 2015)*
	Ang-(1–7)	Peptide	Angiotensin I, II	(Barroso et al., 2017; Magalhaes et al., 2018)
	AnxA1	Protein	–	(Sugimoto, Vago, Teixeira, & Sousa, 2016)*
	DEL-1	Protein	–	(Kourtzelis et al., 2019)
	Galectin-1	Protein	–	(Law, Wright, Iqbal, Norling, & Cooper, 2020; Sundblad, Morosi, Geffner, & Rabinovich, 2017)*
	GILZ	Protein	–	(Vago et al., 2015; Vago et al., 2020)
	SLPI	Protein	–	(Williams, Brown, Roghanian, & Sallenave, 2006)*
	Pla	Protein	Plg	(Carmo et al., 2014; Sugimoto et al., 2017; Sulniute et al., 2016; Vago et al., 2019)
	cAMP	Nucleotide	Adenosine triphosphate	(Tavares et al., 2020)*
	H_2S	Gas	–	(Wallace, Ianaro, Flannigan, & Cirino, 2015)*
	NO	Gas	–	(Wallace, Ianaro, Flannigan, & Cirino, 2015)*
	CO	Gas	–	(Wallace, Ianaro, Flannigan, & Cirino, 2015)*

α-MSH, α-melanocortin-stimulating hormone; AnxA1, Annexin A1; Ang-(1–7), angiotensin 1–7; CO, carbon monoxide; DEL-1, developmental endothelial locus-1; GILZ, Glucocorticoid-induced leucine zipper; H_2S, hydrogen sulfide; MCTR, maresin conjugates in tissue regeneration; NO, nitric oxide; PCTR, protectin conjugates in tissue regeneration; Pla/Plg, plasmin/plasminogen; RCTR, resolvin conjugates in tissue regeneration; SLPI, secretory leukocyte protease inhibitor; SPMs, specialized proresolving mediators. *Review. Table adapted from Sugimoto et al., 2019.

in the host defense against pathogens. In the resolution phase of inflammation, M2 macrophages are predominant and exhibit high efferocytic capacity and anti-inflammatory/tissue repair properties (Korns, Frasch, Fernandez-Boyanapalli, Henson, & Bratton, 2011; Michlewska, Dransfield, Megson, & Rossi, 2009; Rey-Giraud, Hafner, & Ries, 2012). In addition, further subtypes of macrophage have been described (Ariel & Serhan, 2012; Bystrom et al., 2008). In the resolution phase of inflammation, resolving macrophages (Mres) exhibit anti-fibrotic and antioxidant properties that limit tissue oxidative damage and fibrosis (Butenko et al., 2020). They have also been described as important for signaling for post-resolution lymphocyte repopulation during self-limiting inflammation (Bystrom et al., 2008). Unlike M2 macrophages, Mres macrophages are not essential for the clearance of apoptotic cells (designated as "satiated" macrophages) (Schif-Zuck et al., 2011). Mres have been considered distinct from both M1 and M2 macrophages, exhibiting decreased levels of the pro-fibrotic enzyme arginase-1 (an M2 marker) and increased 12/15-lipoxygenase, an enzyme responsible for SPMs synthesis (Schif-Zuck et al., 2011).

Members of the TAM family are critical regulators of efferocytosis, with their ligands forming a bridge between apoptotic cells and macrophages (van der Meer et al., 2014). Importantly, the efferocytosis of apoptotic cells prevents the release of phlogistic intracellular contents and, consequently, secondary necrosis, which can contribute to the development of chronic diseases and autoimmunity (Nathan & Ding, 2010). In fact, the defective clearance of apoptotic cells and, consequently, a failure to resolve inflammation have been associated with the development of many chronic inflammatory and autoimmune diseases, including systemic lupus erythematosus, rheumatoid arthritis, asthma, and atherosclerosis (Grabiec et al., 2017; Kojima, Weissman, & Leeper, 2017; Shao & Cohen, 2011; Waterborg et al., 2018). The chronic inflammatory process is characterized by continued production of pro-inflammatory cytokines, growth factors, persistent recruitment, and permanence of mononuclear cells (macrophages and lymphocytes) in tissues. However, the profile of cells and molecules may vary depending on the disease (Schett & Neurath, 2018). In contrast to acute inflammation, where the resolution process is better understood, the resolution of chronic inflammation still needs extensive investigation. In this context, the pathophysiology of each disease should be considered (Schett & Neurath, 2018). Since the concept of resolution of inflammation is relatively new, there is still no pro-resolving factors in clinical use. However, basic, translational, and clinical studies have demonstrated the effectiveness and potency of pro-resolving mediators to control a vast number of inflammatory conditions, providing a glimpse of the development of resolution-based drugs as a part of resolution pharmacology (Perretti, Leroy, Bland, & Montero-Melendez, 2015).

4. The anti-inflammatory properties of the TAM family

Identification of the intracellular signaling pathways upon TAM activation is fundamental for understanding how their ligands control inflammation, but it is also important to discriminate signaling events following TAM activation by each ligand. Several *in vitro* and *in vivo* studies examine the anti-inflammatory actions of TAM activation by up-regulating suppressor of cytokine signaling (SOCS)1/3 expression (Degboe et al., 2019; Jiang et al., 2019; Mulla et al., 2018; Peng et al., 2019; van den Brand et al., 2013), a well-known cytoplasmic molecule that negatively regulates JAK-STAT signaling of certain pro-inflammatory cytokines (Krebs & Hilton, 2001). However, the dependence on SOCS1/3 for the anti-inflammatory effects of TAM is still debatable. For instance, while SOCS3 was required for downregulating the production of pro-inflammatory cytokines upon TAM stimulation in human monocyte-derived macrophages (Zheng, Hedl, & Abraham, 2015), this dependence was not seen to occur *in vivo* when the blockade of Axl did not worsen lung inflammation in a murine model of ventilator-induced lung injury, even with locally downregulated SOCS3 expression (Otulakowski, Engelberts, Post, Masterson, & Kavanagh, 2018). Thus, the true dependence on the SOCS1/3 pathway for the anti-inflammatory effects of TAM need to be better clarified. Perhaps these different responses occur in a "biased manner", varying according to the TAM ligands, receptors, or systems (cell type, organs, or stimuli).

Macrophages are fundamental cells that participate in virtually all types of inflammatory conditions, and a considerable amount of knowledge regarding the anti-inflammatory functions of TAM family members has come from studies using these cell types. Resident mouse peritoneal macrophages expressed basal levels of Axl and MerTK and their cognate ligands, while Tyro3 was not detected in the absence of previous stimulation (Deng, Zhang, Chen, Yan, & Han, 2012). Still, mouse lung-resident macrophages constitutively expressed both Axl and MerTK, and the Gas6 protein present in these cells seemed to be constitutively bound to Axl, since Axl-deficient cells lost Gas6 detection on the cell membrane (Fujimori et al., 2015). Functionally, exogenous and endogenous Gas6 and Pros1 counterbalanced the production of pro-inflammatory cytokines (TNF, IL-6, and IL-1β) upon LPS stimulation (Deng et al., 2012). Gas6 expression is downregulated following LPS or TNF stimulation of murine peritoneal macrophages (Feng et al., 2011), and THP-1 cells over-expressing Axl produced less TNF and IL-6 in response to LPS when compared with non-transfected cells (Brenig et al., 2020). Although the TLR agonist decreased TAM ligands expression, the remaining Gas6 is still active as a negative feedback control, avoiding excessive production of pro-inflammatory molecules (Zhang et al., 2016). In the mouse macrophage cell line RAW264.7, lipoteichoic acid, a TLR2 agonist, led to the phosphorylation of MerTK and its downstream signaling cascade events, such as AKT phosphorylation and SOCS3 synthesis upon residual endogenous Gas6 action. The blockade of MerTK reduced these events, upregulating NF-κBp65 and the production of TNF and IL-6 (Zhang et al., 2016). Gas6-MerTK also reduced NF-kBp65 activation upon LPS stimulation in RAW264.7 cells. Interestingly, the autophosphorylation site Tyr-867 of MerTK is fundamental in efferocytosis but not in the reduction of LPS-induced NF-κBp65 activation (Tibrewal et al., 2008). Considering the critical role of efferocytosis in trigger events for the resolution of inflammation, distinct Gas6-MerTK downstream signaling may dissociate its anti-inflammatory and pro-resolving properties.

Different studies also show that TAM controls inflammasome activation, an important component of the innate immunity system that recognizes endogenous or microbial patterns, leading to the cleavage and release of the mature forms of IL-1β and IL-18 through the activation of inflammatory caspases (Rathinam & Fitzgerald, 2016). Murine peritoneal macrophages treated with Gas6 decreased caspase-1 activation and IL-1β release upon stimulation with ATP, a classical NLRP3 inflammasome activator. Mechanistically, Gas6 ligation to Axl stimulates autophagy in these cells, a well-known intracellular event that prevents mitochondrial dysfunction, reducing the release of endogenous inflammasome agonists such as reactive oxygen species and oxidized mitochondrial DNA (Deretic & Levine, 2018; Han et al., 2016). *In vivo*, intraperitoneal injection of LPS in Axl-deficient mice caused increased caspase-1 activation and release of IL-1β and IL-18 by Kupffer cells as compared to WT cells, worsening liver inflammation and damage (Han et al., 2016). Gas6 also reduced the release of IL-1β by THP-1 cells after incubation with silica, another well-known NLRP3 inflammasome activator (Shen et al., 2016). Although not using macrophages, Cross et al. also demonstrated that Gas6, possibly binding to Axl and MerTK, decreased IL-1β cleavage, an indication of reduced inflammasome activation, in a fetal membrane upon co-stimulation with viral infection and bacterial products, events associated with preterm premature rupture of membranes and preterm birth (Cross et al., 2017). Thus, these studies support the contribution of TAM family members in controlling inflammation by reducing inflammasome activation, evidencing an important anti-inflammatory arm of these molecules.

Overall, these studies clearly demonstrate the effective contribution of TAM family members to decreasing the production of pro-inflammatory mediators in different cell types and conditions. Although TAM activation is potentially enhanced once bound to phosphatidylserine, all studies mentioned in this topic did not associate the anti-inflammatory effects of TAM with the presence of phosphatidylserine (regardless of whether it was given exogenously or endogenously expressed by any of the studied cells). Thus, the selected studies aimed for an unbiased analysis of the anti-inflammatory properties of TAM, considering the crucial involvement of phosphatidylserine-expressing cells for the resolution of inflammation.

The anti-inflammatory properties of TAM have also been reinforced by studies on cancer. Tumors present multiple mechanisms to evade the immune response, dampening the pro-inflammatory milieu and favoring a pro-tolerogenic environment. The mechanisms of tumor immune escape are complex and include T cell anergy and apoptosis, an increased number of Treg cells, the immature/tolerogenic phenotype of dendritic cells, the presence of tumor-associated macrophages (M2-like profile), and others, that together contribute to tumor growth and metastasis (Seliger, 2005). TAM receptors have been associated with tumor progression, as the TAM family members promote growth, cell survival, migration, and therapy resistance in several cancers (Burstyn-Cohen & Maimon, 2019). Indeed, TAM receptors switch macrophages from the M1 phenotype (anti-tumor) to the M2 (pro-tumor) phenotype (Schoumacher & Burbridge, 2017), which favors tumor progression and metastasis. Of note, TAM inhibitors have exhibited antitumor activities and clinical studies have been conducted evaluating TAM and Axl inhibition therapeutically (Zhu, Wei, & Wei, 2019).

5. Pro-resolving properties of TAM receptor family members

5.1. TAM receptors in efferocytosis and the impact on macrophage polarization

The efferocytic capacity of macrophages may vary among their subtypes in the tissue. For instance, M2 macrophages are generally accepted to be more effective in the clearance of apoptotic cells, since they exhibit a greater efferocytic ability than M1 macrophages (Korns et al., 2011; Michlewska et al., 2009; Montoya et al., 2019; Rey-Giraud et al., 2012). Perhaps the best known contribution of TAM receptors to the resolution of inflammation is their remarkable role in efferocytosis, in which their ligands Gas6 and Pros1 present different binding sites for their receptors and for phosphatidylserine on the apoptotic cell surface (van der Meer et al., 2014). The phagocytosis of apoptotic cells is critical for the resolution of inflammation, eliminating the excessive number of dead PMNs in the site of inflammation, consequently cleaning up eventual inflammatory late apoptotic cells and promoting the differentiation of anti-inflammatory and pro-resolving macrophages.

The expression of TAM receptors varies in distinct subsets of macrophages, with higher levels of expression described in the M2 phenotype. It has been shown that M2-like BMDMs (IL-4 and IL-13 stimulation) exhibit increased levels of *Axl* and *Mertk* mRNA compared to M1 polarized cells (LPS and IFN-γ stimulation) (Shibata et al., 2014). The secretion of Gas6 is also enhanced by IL-4-differentiated M2 from BMDMs (Nepal et al., 2019). In a similar way, MerTK protein levels are increased by M2-like polarizing agents, including M-CSF, IL-4, IL-10, and dexamethasone (Grabiec, Goenka, Fife, Fujimori, & Hussell, 2018; McColl et al., 2009; Zagorska, Traves, Lew, Dransfield, & Lemke, 2014; Zizzo & Cohen, 2018; Zizzo, Hilliard, Monestier, & Cohen, 2012). The polarization of human monocyte-derived macrophages with M-CSF also increases the mRNA levels of *Axl* and *Gas6* (Waterborg et al., 2019). MerTK and Axl have also been associated with a switch of macrophages in tumors from the M1 phenotype to the M2 phenotype (Schoumacher & Burbridge, 2017). On the other hand, lower expression of MerTK and Axl has been associated with M1 polarization (Grabiec et al., 2018; Shibata et al., 2014; Zizzo et al., 2012; Zizzo & Cohen, 2018). However, while some studies have shown a downregulation of Axl in M1 macrophages, there is also evidence of the increased expression of Axl after M1 polarization. For instance, the treatment of BMDMs with the M1 stimulant LPS and IFN-γ increases Axl expression (Zagorska et al., 2014). During M2 polarization with dexamethasone, macrophages exhibit lower Axl protein levels, while MerTK expression is increased (Zagorska et al., 2014). In this study, the authors demonstrated that Axl and MerTK display divergent profiles of expression in inflammatory *versus* tolerogenic settings, respectively.

Both Gas6 and Pros1 actively favor the shift of macrophage polarization from the M1 phenotype to the M2 phenotype. It has been shown that Gas6 induces increased levels of *CD206* and *IL-10* mRNA (M2 markers) in M1-polarized THP-1 macrophages, while the inhibition of Gas6 by neutralizing antibodies decreased the expression of these markers (Nam et al., 2018). In addition, the activation of either MerTK or Tyro3 by Pros1 decreased the expression of M1 gene markers *IL-1*, *IL-6*, and *CD86* in M1-polarized macrophages (Ubil et al., 2018). Consistently, peritoneum macrophages from *Pros1*$^{-/-}$ *mice* exhibited a reduced capacity to convert to the M2 phenotype *in vivo* (Lumbroso et al., 2018). Similar findings were demonstrated in *Gas6*$^{-/-}$ and *Axl*$^{-/-}$/*Mertk*$^{-/-}$ BMDMs (Bosurgi et al., 2017). Fig. 3 summarizes the crosstalk between TAM and their ligands on macrophage polarization.

5.2. TAM receptor activation favors the resolution of acute inflammation and the production of pro-resolving mediators

During inflammatory responses, efficient efferocytosis may reprogram macrophages from a pro-inflammatory to an anti-inflammatory/pro-resolving state (Ariel & Serhan, 2012). By applying a model of peritonitis induced by zymosan, Lumbroso et al. demonstrated that *Pros1* mRNA is upregulated in macrophages from the resolution phase of inflammation (66 h after challenge) when compared to resident macrophages (present at 0 h) from the inflammatory or early resolution phase (24 h after challenge). Moreover, Pros1-deficient macrophages

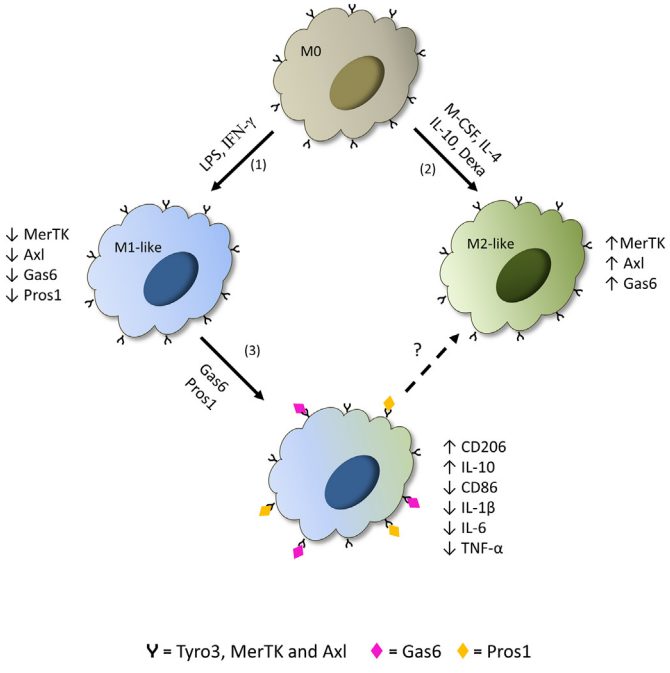

Fig. 3. Crosstalk between TAM receptors and their ligands on macrophage polarization. M1-like macrophages display decreased expression of MerTK, Axl, Gas6, and Pros1 **(1)**. M2-like macrophages exhibit increased expression of MerTK, Axl, and Gas6 **(2)**. TAM binding by Gas6 or Pros1 dampens M1-like macrophage markers (CD86, IL-1β, IL-6, and TNF-α) and consequently promotes the M2-like polarization phenotype (increasing CD206 and IL-10) **(3)**.

display a reduced ability to take up apoptotic neutrophils. The lack of Pros1 in macrophages also reduced their capacity to mature and convert to the M2-like and Mres phenotypes during the resolution of inflammation. Furthermore, Pros1 deficiency resulted in reduced production of the SPM resolvin D1 (RvD1) (Lumbroso et al., 2018). In addition, RvD1 has also been associated with increased expression of MerTK in macrophages (Cai et al., 2017; Li et al., 2013), creating positive feedback for the resolution of inflammation.

For a proper resolution of inflammation, the clearance of apoptotic PMN is fundamental. In a previous study, McColl et al. demonstrated that, under glucocorticoid treatment (a potent anti-inflammatory agent), apoptotic neutrophils specifically bind to Pros1 during efferocytosis mediated by macrophages, reinforcing the notion that Pros1 is a potential target for promoting the resolution of inflammatory responses (McColl et al., 2009). More recently, in a self-resolving model of acute lung injury induced by LPS, Gas6 protein levels were increased in alveolar macrophages during the resolution phase of inflammation (48–72 h after challenge) (Nepal et al., 2019). Gas6 expression was fundamental for efferocytosis of apoptotic neutrophils and consequently for the resolution of inflammation. In this study, the authors conclude that the increased expression of Gas6 was dependent on the activation of the STAT6 transcription factor (convey the signaling for the M2-like induced phenotype), and that the resolution induced by Gas6 was accompanied by the temporal transition of alveolar macrophages to an anti-inflammatory phenotype (Nepal et al., 2019). Gas6 has also been associated with increased levels of SPMs in human monocyte-derived macrophages, including LXA4 and RvD1 (Cai et al., 2016).

In addition to TAM ligands Pros1 and Gas6, further studies evaluated the connection between MerTK activation and the synthesis of pro-resolving mediators. In a sterile model of zymosan-induced peritonitis, increased protein levels of MerTK were found in peritoneal macrophages, the spleen, and lungs during the resolution phase of inflammation (72 h after the challenge) (Choi et al., 2015). Furthermore, the levels of phosphorylated MerTK increased at this time point, suggesting the pronounced activation of this receptor in the resolution phase. In fact, Gas6 protein levels were increased in parallel with MerTK phosphorylation. Consistently, exacerbated inflammatory response was observed in MerTK-deficient mice or by the use of anti-MerTK neutralizing antibody (Choi et al., 2015). Delayed resolution of inflammation in MerTK-deficient mice was associated with impaired efferocytosis of PMN. Importantly, MerTK-deficient mice exhibited lower levels of several SPMs, including RvD1–6, RvE1, RvE3, LXA4, 15-epi-LXA4, LXB4, 15-epi-LXB4, LXB4 isomer, Mar2, 17R-PD1, and 10S,17S-diHDHA in peritoneal exudates, after peritonitis induced by zymosan (Cai et al., 2016).

The metalloproteinase ADAM17 has been described to be responsible for the proteolytic cleavage of TAM receptors in an inflammatory milieu (Guo et al., 2002; O'Bryan et al., 1995; Thorp et al., 2011). This process causes the shedding of soluble forms of these receptors (Guo et al., 2002; O'Bryan et al., 1995). Soluble TAM receptors may competitively inhibit the interaction of membrane receptors with their ligands Gas6 and Pros1 (Ekman, Stenhoff, & Dahlback, 2010; Sather et al., 2007). Interestingly, the pro-resolving mediator RvD1 has been implicated with the prevention of MerTK cleavage (Cai et al., 2017). To better understand the impact of MerTK cleavage on resolution, a model of MerTK cleavage-resistant mice was established (Cai et al., 2016). In this study, Cai et al., showed that the impairment in the cleavage of MerTK accelerates the resolution of peritonitis induced by zymosan. This effect was associated with enhanced efferocytosis of apoptotic PMNs and increased levels of SPMs (Cai et al., 2016). In addition, the same study showed that MerTK is pivotal in reducing tissue damage. By applying a model of ischemia and reperfusion injury, the authors showed that lung injury is enhanced in MerTK-deficient mice and, on the other hand, is reduced in MerTK cleavage-resistant mice (Cai et al., 2016). Collectively, the authors showed that MerTK cleavage limited its pro-resolving actions, including efferocytosis and SPM synthesis.

Additional findings that reinforce the interrelation between TAM and pro-resolving mediators also come from other studies of sterile inflammation (Triantafyllou et al., 2018). Triantafyllou et al. demonstrated that resolution-like MerTK^{+}HLA^{-}DR^{high} monocytes and hepatic macrophages are expanded in the liver of patients with acute liver failure (Triantafyllou et al., 2018). A similar pattern of cells was found in an experimental model of acute liver injury (ALI) induced by acetaminophen, where these cells exhibited enhanced efferocytic capabilities during the resolution phase of inflammation. Consistently, the lack of MerTK results in a significantly higher and persistent degree of ALI. Finally, the authors provide evidence that MerTK^{+} macrophages in the liver is enhanced by the secretory leucocyte protease inhibitor (SLPI), a pro-resolving mediator, which promotes hepatic resolution by suppressing neutrophil activation and promoting their clearance *via* MerTK^{+} macrophages (Triantafyllou et al., 2018). Altogether, these studies provide evidence that TAM family and their ligands have an important effect on the production of pro-resolving mediators and *vice-versa* (Fig. 4). Thus, we suggest that pro-resolving mediators and TAM receptors act mutually in positive feedback, favoring a pro-resolution milieu and accelerating the end of inflammation.

6. TAM receptor activation as a promising anti-inflammatory/pro-resolving therapeutic strategy

Based on the aforementioned studies, the cell-based assays demonstrate how TAM family members could contribute to the fine-tune regulation of inflammatory responses. Using genetic or pharmacological *in vivo* approaches, many works have evidenced the importance of TAM family members in the control of inflammatory diseases. The disturbance of homeostasis during diseases strengthens the important involvement of TAM receptors and their ligands in inflammation. Mice deficient for one or more TAM members normally present an exacerbated inflammatory response in different models of inflammation (Rothlin et al., 2015). For instance, MerTK-deficient (Waterborg et al., 2018) and Axl-deficient mice (Degboe et al., 2019) presented exaggerated joint inflammation when compared to WT mice in serum transfer model of arthritis. Local injection of adenoviruses to overexpress Gas6 and Pros1 reduced the production of pro-inflammatory cytokines and metalloproteinase in the joints, ameliorating tissue inflammation and damage in a collagen-induced arthritis model (van den Brand et al., 2013). Adenoviral overexpression of Pros1 also decreased inflammation and cartilage and bone erosion in serum transfer model of arthritis (Waterborg et al., 2018). In humans, Gas6 is reduced in the serum of rheumatoid arthritis patients (RA) when compared to healthy controls, particularly in erosive RA patients (Bassyouni, El-Wakd, Azab, & Bassyouni, 2017). In addition, elevated levels of soluble Tyro3 in serum and synovial fluid were positively associated with higher disease severity in RA patients (Vullings et al., 2020; Xu et al., 2018). Interestingly, M1-differentiated macrophages isolated from RA patients or healthy controls had decreased expression of MerTK, while M2-like macrophages showed the opposite (Degboe et al., 2019). Anti-TNF agents, which are successfully used for RA treatment, not only increased MerTK expression in RA macrophages but also avoided the decreased expression of Gas6 in M1-like cells. This mechanism was dependent on IL-10-STAT3, since anti-IL-10 treatment reduced anti-TNF-induced MerTK expression (Degboe et al., 2019).

Exogenous Gas6 or Pros1 proved to be effective in reducing inflammation and tissue damage in several animal models of diseases. Systemic injection of Gas6 reduced kidney inflammation, damage, and dysfunction in models of renal ischemia and reperfusion injury and sepsis in mice (Chen et al., 2016; Giangola et al., 2015). Particularly in cecal ligation and puncture model of sepsis, a model associated with marked systemic inflammation, Gas6 treatment improved the survival rate, decreased the levels of pro-inflammatory cytokines (IL-6 and IL-17) in the serum, and reduced inflammation and damage in the lungs and kidneys (Chen et al., 2016; Giangola et al., 2013; Ni et al., 2019). *In vitro*,

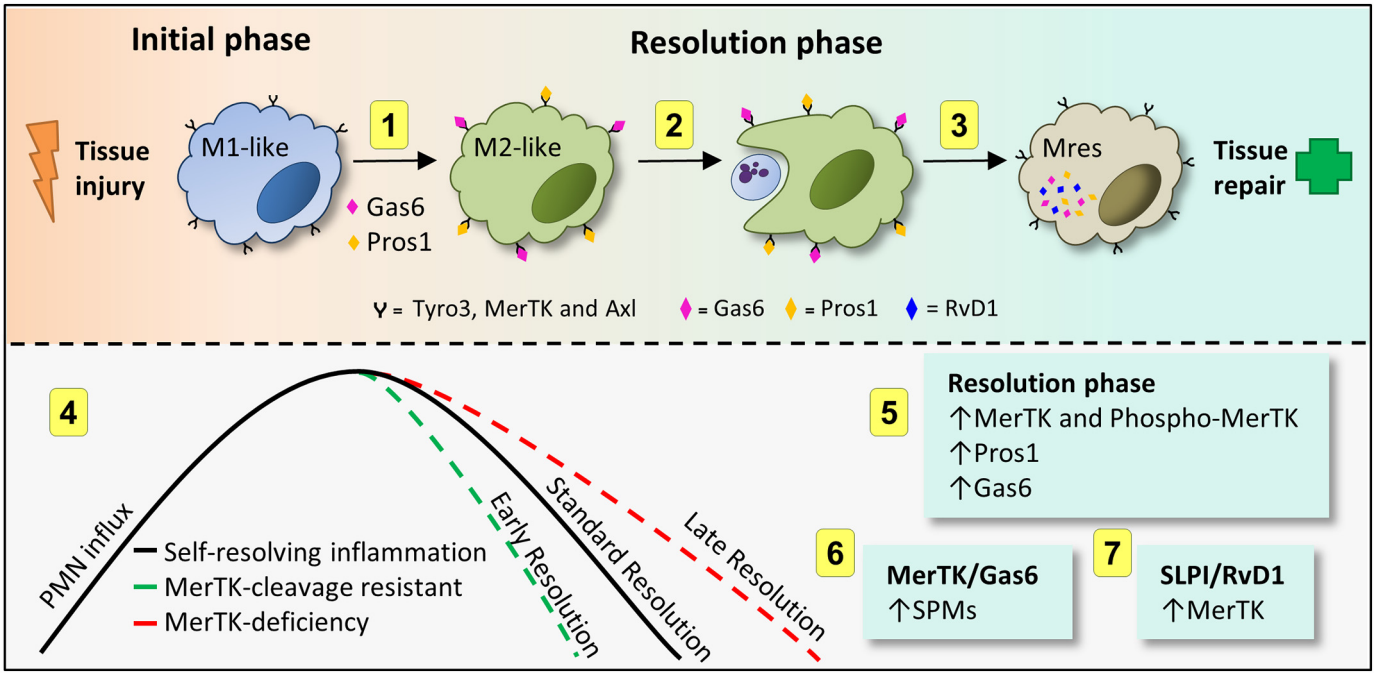

Fig. 4. Contribution of TAM receptors and their ligands to the resolution of acute inflammation. *Upper panel*—Pros1 and Gas6 favor M2 macrophage polarization **(1)**. Activation of TAM by Pros1 and Gas6 enhances the clearance of apoptotic cells *via* efferocytosis **(2)**. The efferocytosis reprograms macrophages to a resolving phenotype (Mres). Macrophages from the resolution phase exhibit higher expression of Pros1, Gas6, and RvD1 **(3)**. *Bottom panel*—The self-resolving inflammation is delayed in the absence or MerTK blockade, while the resolution is accelerated when MerTK is resistant to cleavage **(4)**. MerTK, MerTK phosphorylation, Gas6, and Pros1 are upregulated in the resolution phase of inflammation **(5)**. MerTK and Gas6 increase the production of SPMs **(6)**. The pro-resolving mediators SLPI and RvD1 increase MerTK expression **(7)**.

Table 2
Therapeutic administration of Gas6 and Pros1 for the control of complex inflammatory diseases.

Animal models	Therapeutic strategy	Outcome/effect	Reference
Acute lung injury (induced by IRI) - rat	Recombinant Gas6 (1.25, 2.5, or 5 μg/rat *via* the perfusate)	↓ pro-inflammatory cytokines (TNFα, IL-1β, IL-6) ↓ CXCL-1, TRAF6 and NF-κB ↓ lung edema, neutrophil infiltration, lung injury	(Peng et al., 2019)
Acute kidney injury (induced by CLP) - mouse	Recombinant Gas6 (posttreatment, 3 μg/mouse, systemic injection)	↓ creatinine and blood urea nitrogen ↓ kidney apoptotic cells, inflammation and damage ↑ survival rate	(Chen et al., 2016)
Arthritis (CiOA) - mouse	Gas6 and Pros1 overexpression (Adenovirus)	↓ pro-inflammatory cytokines (IL-12, IL-23, IFNγ, IL-17, TNFα, IL-1β, IL-6) ↓ metalloproteinase (MMP9, MMP13, MMP14) ↓ joint inflammation and damage	(van den Brand et al., 2013)
Arthritis (KRN serum transfer) - mouse	Pros1 overexpression (Adenovirus)	↓ pro-inflammatory cytokines (CCL2, TNFα, IL-1β) ↓ metalloproteinase (MMP3, MMP13, MMP14) ↓ joint inflammation, cartilage and bone erosion	(Waterborg et al., 2018)
IRI (hepatic) - mouse	Recombinant Gas6 (15–20 min pretreatment, 5 μg/mouse, systemic injection)	↓ pro-inflammatory cytokines (TNFα, IL-1β) ↓ ALT, AST ↓ liver damage	(Llacuna et al., 2010)
IRI (renal) - mouse	Recombinant Gas6 (1 h pretreatment, 5 μg/mouse, systemic injection)	↓ pro-inflammatory cytokines (TNFα, IL-1β, IL-6, KC, MIP-2) ↓ NF-κB, iNOS, COX-2 ↓ creatinine and blood urea nitrogen ↓ kidney inflammation, damage and dysfunction	(Giangola et al., 2015)
Sepsis (CLP) - mouse	Recombinant Gas6 (posttreatment, 5 μg/mouse, systemic injection)	↓ pro-inflammatory cytokines (IL-6, IL-17) ↓ AST, ALT, LDH ↓ lung inflammation and damage ↑ survival rate	(Giangola et al., 2013)
Sepsis (CLP) - mouse	Recombinant Gas6 (posttreatment, 6 μg/mouse, systemic injection)	↓ NF-κB ↓ lung and kidney inflammation, vascular hyperpermeability and damage	(Ni et al., 2019)
Sepsis (cecal slurry) - mouse	Recombinant Gas6 (~23 h posttreatment, 5 μg/mouse, systemic injection)	↑ mouse vitality ↓ iNOS, ALT and LDH ↓ lung and kidney damage	(Salmi et al., 2021)
Periodontitis - rat	Recombinant Pros1 (daily, 20 μg/mouse, subcutaneous injection)	↓ pro-inflammatory cytokines (TNFα, IL-6, RANKL) ↓ metalloproteinase (MMP2, MMP9) ↓ alveolar bone loss and osteoclastogenesis	(Jiang et al., 2019)

AST, aspartate aminotransferase; ALT, alanine aminotransferase; CiOA, collagen-induced arthritis; CLP, cecal ligation and puncture; IRI, *ischemia-reperfusion injury;* LDH, lactate dehydrogenase; TgAb, thyroglobulin antibody.

exogenous Gas6 decreased LPS-induced permeability in endothelial cell lines, preserving regular levels of tight junction proteins mainly through Axl activation (Ni et al., 2019). Considering the elementary involvement of endothelial cell activation from the very early events in inflammatory responses, Gas6 protected endothelial cell apoptosis (O'Donnell, Harkes, Dougherty, & Wicks, 1999), reduced endothelial–neutrophil interaction in the presence of pro-inflammatory molecules (Avanzi et al., 1998), and decreased chemotaxis of neutrophil-like HL-60 cells upon CXCL8/IL-8 stimulation (Giangola et al., 2013). Thus, the anti-inflammatory properties of TAM family members occur in multiple instances in inflammation, acting in different cell types, tissues, and moments. *In vivo* studies related to therapeutic administration of Gas6 and Pros1 for the control of complex inflammatory diseases are listed in Table 2.

More recently, some studies have also demonstrated the interplay between TAM and pro-resolving mediators in models of chronic inflammation. Rymut et al. demonstrated that impaired efferocytosis in aged mice is reversed under RvD1 treatment. Mechanistically, RvD1 regulates senescent cell-induced MerTK cleavage (Rymut et al., 2020). In the context of RA, Alivernini et al. showed that RvD1 is released by MerTK^{+} synovial tissue macrophages, and that concentrations of RvD1 were significantly high in culture supernatants of synovial tissue macrophages from patients in remission (Alivernini et al., 2020).

On the other hand, the knowledge about the anti-inflammatory/pro-resolving effects of TAM and their therapeutic use must be carefully analyzed in the contexts of infections, particularly viral infections. Regarding this point, TAM family modulation could be closely related to COVID-19 pathophysiology, linked to either immunothrombosis or hyperinflammation associated with disease severity in some patients infected with SARS-CoV-2. Indeed, TAM ligands display important effects on the blood coagulation system, as Gas6 displays a procoagulant effect while Pros1 is anticoagulant (Law, Graham, Di Paola, & Branchford, 2018). In addition, TAM receptors have been described to contribute to virus entry into the cells in some diseases, such as Dengue, Zika, and Ebola (Z. Y. Wang, Wang, & An, 2020). In fact, Axl inhibition has been considered a possible alternative for COVID-19 treatment (Bouhaddou et al., 2020; S. Wang et al., 2021) due to the antiviral activities reported in preclinical studies. However, TAM inhibition should be performed with caution since TAM anti-inflammatory/pro-resolving effects might also be affected. Thus, the impact of the TAM family on the control of COVID-19 should be addressed in further studies.

7. Concluding remarks

The development of regulatory agents to control excessive or persistent inflammation carrying minimal or no side effects is continuous and faces considerable demands. While anti-inflammatory compounds are widely used to treat acute and chronic inflammation, the use of pro-resolving mediators is still in development but already represents a promising strategy to revolutionize the way of controlling inflammatory disorders. TAM receptor activation embraces both concepts and could provide the desired equilibrium to address inflammation, effectively leading to its proper ending and promoting tissue healing. Although pre-clinical studies are promising as exemplified above, there are broad and important issues related to effectiveness and safety, mainly considering immunosuppression and actions in chronic and infectious inflammation, experimental and clinically. The clear identification of intracellular signaling pathways following TAM activation is fundamental for improving the basic knowledge of the anti-inflammatory and pro-resolving actions of TAM family members for the control of inflammatory diseases, also considering the identification of possible ligand, receptor, and tissue bias.

Conflict of interest statement

The authors declared no conflict of interests.

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