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Biology of the TAM Receptors

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The TAM receptors—Tyro3, Axl, and Mer—comprise a unique family of receptor tyrosine kinases, in that as a group they play no essential role in embryonic development. Instead, they function as homeostatic regulators in adult tissues and organ systems that are subject to continuous challenge and renewal throughout life. Their regulatory roles are prominent in the mature immune, reproductive, hematopoietic, vascular, and nervous systems. The TAMs and their ligands—Gas6 and Protein S—are essential for the efficient phagocytosis of apoptotic cells and membranes in these tissues; and in the immune system, they act as pleiotropic inhibitors of the innate inflammatory response to pathogens. Deficiencies in TAM signaling are thought to contribute to chronic inflammatory and autoimmune disease in humans, and aberrantly elevated TAM signaling is strongly associated with cancer progression, metastasis, and resistance to targeted therapies.

The name of the TAM family is derived from the first letter of its three constituents—Tyro3, Axl, and Mer (Prasad et al. 2006). As detailed in Figure 1, members of this receptor tyrosine kinase (RTK) family were independently identified by several different groups and appear in the early literature under multiple alternative names. However, Tyro3, Axl, and Mer (officially c-Mer or MerTK for the protein, *Mertk* for the gene) have now been adopted as the NCBI designations. The TAMs were first grouped into a distinct RTK family (the Tyro3/7/12 cluster) in 1991, through PCR cloning of their kinase domains (Lai and Lemke 1991). The isolation of full-length cDNAs for Axl (O'Bryan et al. 1991), Mer (Graham et al. 1994), and Tyro3 (Lai et al. 1994) confirmed their segregation into a structurally distinctive family of orphan RTKs (Manning et al. 2002b). The two ligands that bind and activate the TAMs—Gas6 and Protein S (Pros1)—were identified shortly thereafter (Ohashi et al. 1995; Stitt et al. 1995; Mark et al. 1996; Nagata et al. 1996).

Subsequent progress on elucidating the biological roles of the TAM receptors was considerably slower and ultimately required the derivation of mouse loss-of-function mutants (Camenisch et al. 1999; Lu et al. 1999). The fact that *Tyro3*$^{-/-}$, *Axl*$^{-/-}$, and *Mer*$^{-/-}$ mice are all viable and fertile permitted the generation of a complete TAM mutant series that included all possible double mutants and even triple mutants that lack all three receptors (Lu et al. 1999). Remarkably, these *Tyro3*$^{-/-}$*Axl*$^{-/-}$*Mer*$^{-/-}$ triple knockouts (TAM TKOs) are viable, and for the first 2–3 wk after birth, superficially indistinguishable from their wild-type counterparts (Lu et al. 1999). Because many

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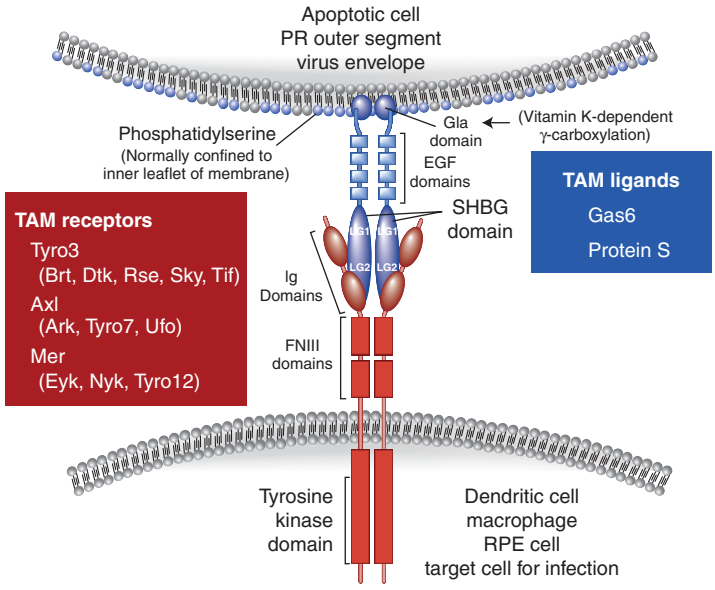

Figure 1. TAM receptors and ligands. The TAM receptors (red) are Tyro3 (Lai and Lemke 1991; Lai et al. 1994)—also designated Brt (Fujimoto and Yamamoto 1994), Dtk (Crosier et al. 1994), Rse (Mark et al. 1994), Sky (Ohashi et al. 1994), and Tif (Dai et al. 1994); Axl (O'Bryan et al. 1991)—also designated Ark (Rescigno et al. 1991), Tyro7 (Lai and Lemke 1991), and Ufo (Janssen et al. 1991); and Mer (Graham et al. 1994)—also designated Eyk (Jia and Hanafusa 1994), Nyk (Ling and Kung 1995), and Tyro12 (Lai and Lemke 1991). The TAMs are widely expressed by cells of the mature immune, nervous, vascular, and reproductive systems. The TAM ligands (blue) are Gas6 and Protein S (Pros1). The carboxy-terminal SHBG domains of the ligands bind to the immunoglobulin (Ig) domains of the receptors, induce dimerization, and activate the TAM tyrosine kinases. When γ-carboxylated in a vitamin-K-dependent reaction, the amino-terminal Gla domains of the dimeric ligands bind to the phospholipid phosphatidylserine expressed on the surface on an apposed apoptotic cell or enveloped virus. See text for details. (From Lemke and Burstyn-Cohen 2010; adapted, with permission, from the authors.)

RTKs play essential roles in embryonic development, even single loss-of-function mutations in RTK genes often result in an embryonic-lethal phenotype (Gassmann et al. 1995; Lee et al. 1995; Soriano 1997; Arman et al. 1998). The postnatal viability of mice in which an entire RTK family is ablated completely—the TAM TKOs can survive for more than a year (Lu et al. 1999)—is therefore highly unusual. Their viability notwithstanding, the TAM mutants go on to develop a plethora of phenotypes, some of them debilitating (Camenisch et al. 1999; Lu et al. 1999; Lu and Lemke 2001; Scott et al. 2001; Duncan et al. 2003; Prasad et al. 2006). Almost without exception, these phenotypes are degenerative in nature and reflect the loss of TAM signaling activities in adult tissues that are subject to regular challenge, renewal, and remodeling. These activities are the subject of this review.

TAM RECEPTOR/LIGAND STRUCTURE AND SIGNALING FEATURES

The extracellular domains of TAM receptors are composed of two structural modules that are used repeatedly in other RTK ectodomains, but that are configured in a defining two-plus-two combination in the TAMs (Fig. 1). The amino-terminal regions of these ectodomains carry tandem immunoglobulin-related domains that mediate ligand binding (Heiring et al. 2004; Sasaki et al. 2006), which are followed by tandem fibronectin type III repeats (O'Bryan et al. 1991;

Graham et al. 1994; Lai et al. 1994; Lemke and Rothlin 2008). All three TAM receptors have a single-pass *trans*-membrane domain, and all carry a catalytically competent protein-tyrosine kinase (Fig. 1). High-resolution crystal structures have been determined for the Tyro3 (Powell et al. 2012) and Mer kinase domains (Huang et al. 2009; Liu et al. 2012).

In many cells, the activation of this tyrosine kinase is coupled to the downstream activation of the phosphoinositide 3 kinase (PI3K)/AKT pathway. Most of this downstream PI3K signaling is nucleated through a TAM-autophosphorylated Grb2-binding site, which is located 18 residues carboxy terminal to the kinase domain and is conserved in all three TAMs (Fig. 2) (Fridell et al. 1996; Ling et al. 1996; Braunger et al. 1997; Goruppi et al. 1997; Georgescu et al. 1999; Lan et al. 2000; Ming Cao et al. 2001; Son et al. 2007; Tibrewal et al. 2008; Weinger et al. 2008). Coupling to phospholipase C, ERK1/2, Ras, and MAP kinase activation have also been described in many different cells (Keating et al. 2010; Lijnen et al. 2011; Ou et al. 2011). These TAM-activated signaling pathways (Fig. 2), which involve what might be called "the usual suspects" downstream from RTK activation, operate in all TAM-expressing cells. Macrophages, dendritic cells, and other sentinel cells of the immune system, however, also express cytokine receptor signaling systems—in particular, the type I interferon (IFN) receptor—that are directly coupled to, interact with, and are codependent on the TAM receptors. In these cells, the TAM-activated PI3K/AKT pathway is often dominated and obscured by a stronger TAM-activated JAK/STAT signaling pathway (Zong et al. 1996; Rothlin et al. 2007; Lemke and Rothlin 2008). Differential TAM activation of PI3K/AKT versus JAK/STAT signaling may be important for the differential activation of distinct TAM-regulated bioactivities (Fig. 2).

TAM receptors are among the last RTKs to have appeared during evolution (Manning et al. 2002a,b). Unlike the FGFR, EGFR, or ROR families, for example, there are no TAM representatives in either *Drosophila* or *Caenorhabditis elegans*. A single TAM-like receptor gene and a single Gas6/Pros1-like ligand gene are first seen in the genomes of prevertebrate urochordates such as *Ciona* (Kulman et al. 2006; Lemke and Rothlin 2008), coincident with the first appearance of type I and type II cytokines (e.g., interferons) and cytokine receptors.

The two TAM ligands—Gas6 and Pros1 (Manfioletti et al. 1993; Stitt et al. 1995; Mark et al. 1996)—are large (~80-kDa) proteins that are ~42% identical and share the same multidomain arrangement (Fig. 1). They have two unusual structural features that are key to their bioactivities. The first is a carboxy-terminally positioned "sex hormone-binding globulin" (SHBG) domain composed of two laminin G domains (Fig. 1). This SHBG domain binds to the Ig domains of the receptors and induces their dimerization and subsequent kinase activation (Nyberg et al. 1997; Tanabe et al. 1997; Evenas et al. 2000; Sasaki et al. 2002, 2006). The second is a so-called Gla domain positioned at the very amino terminus of both Gas6 and Pros1 (Stitt et al. 1995; Ishimoto et al. 2000; Rajotte et al. 2008). (The SHBG and Gla domains are separated by four EGF-related domains.) This ~60-amino-acid Gla domain is rich in glutamic acid residues whose γ-hydroxyl groups are posttranslationally carboxylated in a vitamin K-dependent modification (Huang et al. 2003; Li et al. 2004; Bandyopadhyay 2008). Gas6 and Pros1 share Gla domains with several proteins of the blood coagulation cascade, such as factors VII, IX, and X (Dahlback 2000; Stafford 2005). Indeed, in addition to acting as a TAM ligand, Pros1 also functions as an anticoagulant in this cascade (Dahlback 2000; Burstyn-Cohen et al. 2009).

γ-Carboxylation of Gla domains allows them to bind to phosphatidylserine (PtdSer). In most cells, the activity of a set of P_4-ATPases—so-called flippases—ensures that this phospholipid is confined to the inner, cytoplasm-facing leaflet of the plasma membrane (van Meer et al. 2008). In activated platelets and apoptotic cells (among other sites), these flippases are disabled such that PtdSer is displayed on the extracellular membrane surface as well. For apoptotic cells (ACs), extracellularly displayed PtdSer is among the most potent "eat-me" signals by which these dead cells are

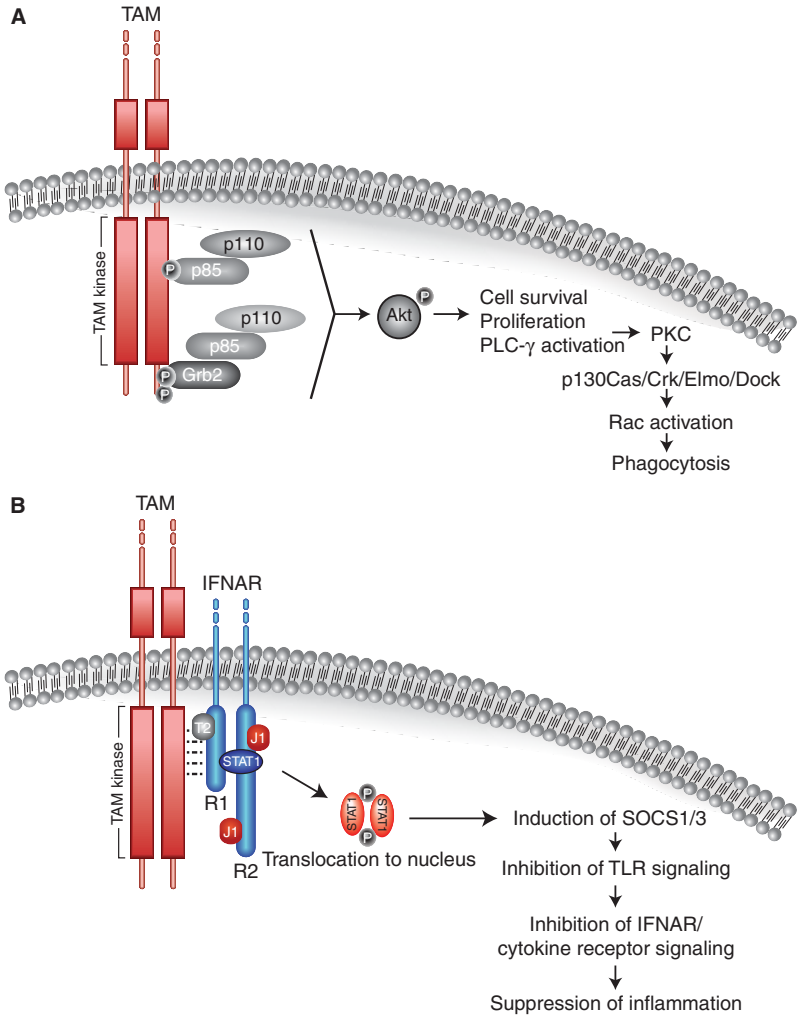

Figure 2. TAM receptor signaling pathways. (*A*) Free TAMs. As receptor dimers, activated TAM proteins drive a conventional RTK signaling pathway that is dominated by the phosphorylation and activation of Akt. The positions of major tyrosine autophosphorylation sites shared between Tyro3, Axl, and Mer are indicated (P). The tyrosine immediately downstream from the kinase domain (Y821 in human Axl) is bound by the SH2 domain of Grb2, which recruits the p85 subunit of PI3 kinase through an SH3 (Grb2)-proline-rich domain (p85) interaction. Alternatively, p85 can bind this phosphotyrosine directly using its own SH2 domain. P85 also binds to the indicated phosphotyrosine within the kinase domain (see, e.g., Weinger et al. 2008). Mobilization of the joint p85/p110 PI3K complex results in the downstream phosphorylation and activation of Akt. Mer activation has also been found to drive the downstream activation of PLC-γ, by a mechanism that is not delineated biochemically (Tibrewal et al. 2008). These pathways are required for TAM regulation of cell survival and the mobilization of the actin cytoskeleton required for the engulfment of apoptotic cells by phagocytes. (*B*) TAM receptors complexed with the type I interferon receptor (IFNAR). In dendritic cells, TAM receptors—when activated by the binding of a TAM ligand—form a coimmunoprecipitable complex specifically with the R1 (or α) chain of the IFNAR (Rothlin et al. 2007). This may be associated with the activation of Jak1 (J1) (Zong et al. 1996). Direct activation of the hybrid TAM-IFNAR receptor by the addition of Gas6 leads to the rapid tyrosine phosphorylation and activation of Stat1. This dimeric transcription factor then translocates to the nucleus, where it drives the expression of the cytoplasmic cytokine inhibitors SOCS1 and 3. This pathway is required for the inhibition of inflammatory responses in dendritic cells (Rothlin et al. 2007; Lemke and Rothlin 2008). See text for details.

recognized by phagocytes (Ravichandran 2010). Gla-domain-containing proteins can therefore bind the surface membranes of ACs. As discussed below, the interaction of the γ-carboxylated amino-terminal Gla domains of Gas6 and Pros1 with a PtdSer-containing membrane is a crucial feature of their activation of TAM receptors, and it is possible that in vivo these ligands *always* signal in the context of membrane association.

As depicted in Figure 1, Gas6 and Pros1 appear to bind to TAM receptors as dimers, and for Pros1, multimerization is required for TAM activation (Uehara and Shacter 2008). Apart from this, receptor–ligand pairing relationships and signaling interactions for the TAM system remain incompletely understood. For example, we do not know the extent to which Pros1 and Gas6 may heterodimerize, and if this occurs, how receptor binding and activation profiles of the heterodimer may differ from those of Gas6 or Pros1 homodimers. Similarly, the extent to which individual TAM receptors may heterodimerize in different cellular settings is also poorly understood. The preponderance of evidence indicates that Gas6 functions as a ligand for all three TAM receptors, with reduced binding affinity for Mer relative to Axl and Tyro3 (Ohashi et al. 1995; Stitt et al. 1995; Mark et al. 1996; Nagata et al. 1996; Chen et al. 1997; Lemke and Rothlin 2008). Pros1, in contrast, appears to bind and activate Tyro3 and Mer, with little or no affinity for Axl (Stitt et al. 1995; Prasad et al. 2006; Lemke and Rothlin 2008; Uehara and Shacter 2008; Zhong et al. 2010). In an active area of research, the extent to which Gas6 and/or Pros1 contribute to the observed activity of specific TAM receptors has just begun to be dissected genetically. As discussed below, the first example of such a differential genetic analysis has recently been reported for Gas6 and Pros1 action in Mer-expressing retinal pigment epithelial cells of the eye (Burstyn-Cohen et al. 2012).

In some settings, the biologically relevant cellular sources of Gas6 and/or Pros1 required for TAM activation also remain to be determined. In several cell types, TAM signaling appears to be autocrine/paracrine, in that a TAM-positive cell has frequently been found to express Pros1 and/or Gas6 (Lu et al. 1999; Prasad et al. 2006; Rothlin et al. 2007). Pros1 is expressed at ~300 nM in the blood, into which it is secreted by hepatocytes and vascular endothelial cells (Burstyn-Cohen et al. 2009). (In contrast, Gas6 is present at ≤0.2 nM in serum, and nearly all of this is complexed with soluble Axl ectodomain [Ekman et al. 2010].) Tyro3- and Mer-expressing cells that transit through the circulation are therefore exposed to saturating levels of Pros1. In the immune system, an important source of Pros1 for TAM-expressing macrophages and dendritic cells (see below) may be activated T cells (Smiley et al. 1997).

TAM MEDIATION OF THE PHAGOCYTOSIS OF APOPTOTIC CELLS

TAM receptor signaling plays an especially important role in the engulfment and phagocytic clearance of apoptotic cells (ACs) and membranes in adult tissues (Lemke and Rothlin 2008; Lemke and Burstyn-Cohen 2010). In this process, a TAM ligand, Gas6 or Pros1, serves as a "bridging molecule" that physically links a TAM receptor, generally Mer or Axl, expressed on the surface of the phagocyte, to PtdSer, which is displayed on the surface of the AC that will be engulfed (Fig. 1) (Wu et al. 2006; Nagata et al. 2010). At the same time, this ligand must also activate the tyrosine kinase activity of the TAM receptor for the process of phagocytosis to go forward (Scott et al. 2001; Mahajan and Earp 2003; Tibrewal et al. 2008; Todt et al. 2008; Lemke and Burstyn-Cohen 2010).

The first phenotype described in the TAM TKOs was male infertility, which is tied to the degenerative death of nearly all germ cells in the testes (Lu et al. 1999). This cell death results from a dramatic pileup of AC corpses in the seminiferous tubules and is degenerative rather than developmental in nature (Lu et al. 1999); this is due to the loss of TAM receptor function in Sertoli cells (Lu et al. 1999; Chen et al. 2009; Sun et al. 2010). These somatic support cells are phagocytes; among their most important roles is the PtdSer-dependent clearance of the enormous number of apoptotic germ cells that are generated during meiosis (Kawasaki et al. 2002).

It has been estimated that more than half of the meiotic population dies during each cycle of mammalian spermatogenesis, and thus the clearance of these AC corpses (on the order of 10^8/d in a human male) by Sertoli cells is critical. This process is TAM dependent; Sertoli cells express all three TAMs and both TAM ligands, and in the absence of TAM signaling, the phagocytosis of apoptotic germ cells in the testes is significantly attenuated (Lu et al. 1999).

A similarly dramatic phenotype is seen in the retina of both TAM TKOs and *Mer*$^{-/-}$ single mutants. These mutants are born with normal retinas, but by 2 mo after birth, most of their photoreceptors (PRs) have died (Lu et al. 1999; Duncan et al. 2003). This is a nonautonomous phenotype with respect to PRs, in that these cells do not express the TAMs. Rather, both Mer and Tyro3 are expressed by cells of the retinal pigment epithelium (RPE) (Prasad et al. 2006). Like Sertoli cells in the testes, RPE cells are phagocytes (Sparrow et al. 2010). Unlike Sertoli cells, however, they do not engulf ACs. Rather, the apical microvilli of these cells engulf and metabolize only part of a living cell—the distal ends of PR outer segments. These outer segments (OS) are the rhodopsin-containing organelles in which light is detected. PRs synthesize and insert new membrane at the proximal base of their OS every day, and the distal tips of these organelles are phagocytozed by RPE cells—also on a daily basis—to remove toxic oxidative products generated by phototransduction and to maintain a constant OS length (Prasad et al. 2006; Coleman et al. 2009; Strick et al. 2009; Nandrot and Dufour 2010). In *Mer*$^{-/-}$ mice, RPE cells differentiate normally but fail to perform this phagocytosis, which leads to the apoptotic death of nearly all PRs (Feng et al. 2002; Duncan et al. 2003). Unlike the situation with germ cells in the testes, PR apoptosis does not occur normally but is instead triggered by the failure of mutant RPE cells to phagocytose PR OS. Consistent with the phenotype of the *Mer*$^{-/-}$ mice, the PR degeneration seen in the *Royal College of Surgeons* rat, a decades-old model of retinitis pigmentosa (Bourne et al. 1938; Edwards and Szamier 1977), has been found to be due to mutation of the rat *Mertk* gene (D'Cruz et al. 2000; Nandrot and Dufour 2010); and in humans, 12 distinct pathogenic sequence variants in the *Mertk* gene lead to inherited forms of retinitis pigmentosa and retinal dystrophy (Gal et al. 2000; Ostergaard et al. 2011). Gas6 and Pros1 have been found to function as independent and interchangeable Mer ligands in this system. Mouse mutants in which all Gas6 or all Pros1 are singly eliminated from the retina have a wild-type number of PRs, but mice in which both Gas6 and Pros1 are removed display PR degeneration that perfectly phenocopies the degeneration seen in *Mer*$^{-/-}$ mice (Burstyn-Cohen et al. 2012).

The TAMs play similarly critical roles in AC clearance by phagocytes of the immune system—most prominently macrophages (Scott et al. 2001). In humans, $>10^9$ ACs are generated every day, but at steady state, these dead cells are nearly impossible to detect. This is because they are almost immediately cleared by macrophages and other phagocytes. In many settings, these cells rely on the eat-me signal PtdSer to recognize dead cells as targets for engulfment (Ravichandran 2010). Phagocytic removal of ACs is also prominent during the resolution phase of inflammation, when large numbers of infiltrating granulocytes and lymphocytes undergo apoptosis and must be cleared to terminate an inflammatory response (Elliott and Ravichandran 2010; Nagata et al. 2010). Incomplete phagocytosis of ACs leads to the accumulation of secondary necrotic cells, which constitute a source of self-antigens. Not surprisingly then, defects in these TAM-dependent processes are associated with the development of human autoimmune diseases (Gaipl et al. 2007; Shao and Cohen 2011), and autoimmune phenotypes are prominent features of the TAM mouse mutants (Scott et al. 2001; Seitz et al. 2007; Ait-Oufella et al. 2008; Thorp et al. 2008; Shao et al. 2009; Lemke and Burstyn-Cohen 2010).

TAM REGULATION OF THE INNATE IMMUNE RESPONSE

Mechanistically linked to their role in the phagocytosis of ACs is the role that the TAMs play in the feedback inhibition of the innate immune

response to pathogens. This important regulatory activity has been studied in both macrophages and dendritic cells (DCs), although the mechanism of inhibition is known in detail only in the latter (Rothlin et al. 2007). DCs and other sentinel cells use Toll-like receptors (TLRs) and other pattern recognition receptors to detect the presence of invariant molecular patterns, such as lipopolysaccharide and double-stranded RNA, which are associated with bacteria, viruses, and other pathogens (Akira 2006; Beutler et al. 2006). Activation of these receptors leads to the production of proinflammatory cytokines such as tumor necrosis factor (TNF) α, interleukin (IL)-6, and type I interferons (Fig. 3) (Iwasaki and Medzhitov 2004). Although these cytokines are required to combat infection, they are powerful agents that must be controlled after the innate immune response is mobilized, because unrestrained cytokine signaling results in chronic inflammation and can lead to a response against self (Marshak-Rothstein 2006).

In DCs, the *Axl* gene is expressed at a modest steady-state level before pathogen encounter but is strongly induced by TLR activation and subsequently by type I IFNs through a JAK-Stat1-dependent mechanism (Rothlin et al. 2007). The up-regulated Axl protein then binds to and co-opts the type I IFN receptor (IFNAR) by forming a complex with the R1 chain of this receptor (Figs. 2 and 3). In so doing, Axl switches the IFNAR signaling modality from proinflammatory to immunosuppressive, by driving the activation of the genes encoding the suppressor of cytokine signaling (SOCS) 1 and 3 (Rothlin et al. 2007; Yoshimura et al. 2007). An SH2 domain of these cytoplasmic inhibitors binds to phosphotyrosine residues in JAK kinases that are associated with the IFNAR and other cytokine receptors (and to phosphorylated tyrosine within the receptors themselves), and a carboxy-terminal SOCS box then mediates proteosomal degradation of associated proteins. The amino-terminal regions of SOCS1 and SOCS3 also contain a kinase-inhibitory region that acts as a JAK pseudosubstrate (Yoshimura et al. 2007; Croker et al. 2008). In this way, the induced SOCS proteins, whose expression in DCs is very largely dependent on activation of the TAM-IFNAR multimeric complex, terminate the inflammatory response to pathogens (Fig. 3) (Rothlin et al. 2007).

This pathway is an important inhibitor of inflammation in DCs and macrophages. The induction of SOCS 1 and 3 by type I IFNs is markedly blunted in Axl-deficient DCs. At the same time, the induction of these proteins by direct activation of the TAM receptors—through addition of Gas6—is equally dependent on the presence of both the IFNAR and associated Stat1 (Rothlin et al. 2007). The co-dependence of the TAM and IFNAR receptor systems for immunosuppression provides an explanation for the long-standing conundrum that type I IFNs can be *both* proinflammatory and immunosuppressive in sentinel cells of the immune system. If a type I IFN binds to the free IFNAR, it delivers a proinflammatory stimulus, but if it binds to the TAM-IFNAR receptor complex, it drives an immunosuppressive response (Fig. 3) (Sharif et al. 2006; Rothlin et al. 2007; Lemke and Rothlin 2008). The provision of an immune stimulus—for example, through activation of TLR4 with LPS—to a TAM-deficient cell or mouse inevitably leads to a hyperelevated inflammatory response (Camenisch et al. 1999; Lu and Lemke 2001; Rothlin et al. 2007). This means that deficiencies in TAM signaling are always associated with sustained immune activation and chronic inflammation.

TAM SIGNALING AND AUTOIMMUNE DISEASE

It is therefore not surprising that mouse mutants in TAM receptor genes eventually develop broad-spectrum autoimmune disease (Lu and Lemke 2001; Scott et al. 2001; Radic et al. 2006; Wallet et al. 2008; Rothlin and Lemke 2010; Shao et al. 2010). This disease, which is particularly severe in $Axl^{-/-}Mer^{-/-}$ double mutants and in TAM TKOs (Lu and Lemke 2001), has clinical features of both systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), and is characterized by swollen joints, IgG deposits in the kidneys and other tissues, and pro-

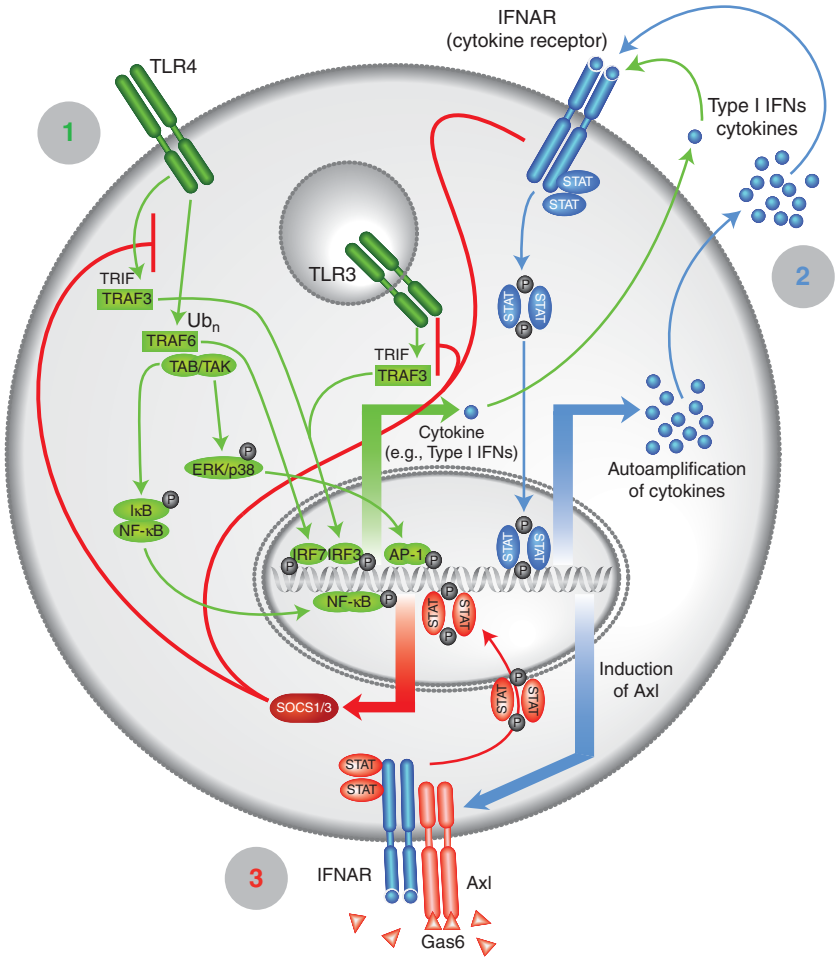

Figure 3. A TAM-regulated cycle of inflammation in dendritic cells. An initial recognition phase (1, green), mediated by Toll-like receptors (e.g., TLR4 on the cell surface and TLR3 in endosomes) and other pattern recognition receptors triggers a kinase cascade that leads to the activation of transcription factors (IRF3/7, AP-1, NF-κB) that drive the production of an initial bolus of type I interferons (IFNs) and other proinflammatory cytokines. In a second response phase (2, blue), the levels of these cytokines are elevated via a feed-forward, JAK-STAT-dependent amplification loop. This same JAK-SAT pathway drives the transcription of the Axl gene. In a final resolution phase (3, red), the induced Axl protein binds to the R1 chain of the type I IFN receptor (IFNAR). The hybrid TAM-IFNAR receptor activates a Stat1 dimer that drives the transcription of the genes encoding SOCS1 and SOCS3. These proteins inhibit both TLR and cytokine receptor signaling, and thereby return the dendritic cell to baseline (Rothlin et al. 2007; Lemke and Rothlin 2008). The features of this self-limiting cycle predict that the provision of an immune stimulus to a dendritic cell with diminished TAM signaling will always result in a hyperelevated inflammatory response. See text for details. (From Rothlin et al. 2007; adapted and reprinted, with permission, from the author.)

nounced splenomegaly and lymphadenopathy. TAM mutant mice also display relatively high titers of antibodies to autoantigens, including double-stranded DNA, phospholipids, and ribonucleoproteins (Lu and Lemke 2001; Scott et al. 2001; Radic et al. 2006). Crossing *Mer* or *Axl* mutants into existing mouse models of autoimmune disease has generally been found to exacerbate disease (Weinger et al. 2011; Ye et al. 2011).

Defects in the clearance of apoptotic cells and unabated type I IFN signaling—both of which are direct consequences of TAM deficiency—are also both thought to drive the development of human autoimmune diseases, including SLE, RA, and inflammatory bowel diseases (IBDs) (Gaipl et al. 2007; Ronnblom and Pascual 2008; Nagata et al. 2010). Correspondingly, several lines of evidence suggest that diminished TAM signaling may contribute to human autoimmunity (Rothlin and Lemke 2010). There is an anecdotal medical literature that ties low circulating levels of Pros1 to IBDs (Song et al. 2000; Zezos et al. 2007; Cakal et al. 2010; Diakou et al. 2011) and a much larger literature that establishes an association between low Pros1 and SLE (Song et al. 2000; Brouwer et al. 2004; Meesters et al. 2007). A recent analysis of a 107-patient SLE cohort found that levels of free protein S—but not Gas6—were significantly lower in SLE patients with a history of serositis, neurologic disorder, hematologic disorder, and immunologic disorder, and that low Pros1 levels were correlated with other disease-associated risk factors such as reductions in the complement proteins C3 and C4 (Suh et al. 2010). Polymorphisms in the *Mertk* gene have been tied to SLE (Cheong et al. 2007), and a clear genetic link has also been made with respect to the development of multiple sclerosis (MS). Here, a large genome-wide association study identified polymorphisms in the *Mertk* gene as risk factors for the development of MS (Ma et al. 2011; Sawcer et al. 2011).

The most widely prescribed drugs used to treat the chronic inflammation associated with many human autoimmune diseases—namely, glucocorticoids (GCs) such as prednisone and prednisolone—have recently been shown to potentiate TAM signaling. One well-described immunosuppressive activity of GCs is their ability to stimulate the phagocytosis of ACs by macrophages (Liu et al. 1999). Agonists for the liver-X-receptor (LXR) family of nuclear hormone receptors display this same activity (A-Gonzalez et al. 2009). Remarkably, the ability of both GCs and LXR agonists to stimulate macrophage phagocytosis of ACs has recently been shown to be due entirely to their ability to up-regulate expression of Mer (A-Gonzalez et al. 2009; McColl et al. 2009). These and related findings suggest that activation of TAM signaling may be therapeutic in the context of autoimmune disease. In this regard, in vivo delivery of adenoviruses expressing either Gas6 or Pros1 has been found to significantly diminish disease symptoms in a mouse model of collagen-induced arthritis (van den Brand et al. 2013).

TAM RECEPTORS AS TARGETS FOR VIRAL INFECTION

A very active area of current research relates to the role of TAM receptors in infection by viruses. In a process termed "apoptotic mimicry" (Mercer and Helenius 2010; Mercer 2011), the eat-me signal PtdSer has been found to be displayed on the extracellular membrane surface of several enveloped viruses, including vaccinia virus, cytomegalovirus, Lassa fever virus, and HIV (Callahan et al. 2003; Mercer and Helenius 2008; Soares et al. 2008). In facilitating infection, the TAMs do not function as direct virus receptors. Rather, Gas6 and Pros1 again serve as "bridging molecules"—this time between a membrane that surrounds a virus capsid and the cell that the virus will infect (Fig. 1).

Tyro3, Axl, and Mer have been found to function as entry factors for the Ebola/Marburg family of hemorrhagic fever filoviruses (Shimojima et al. 2006, 2007). Closely related cell lines that show marked differences in infectivity with pseudotyped viruses containing Ebola or Marburg envelope glycoproteins, or in infectivity with the Zaire or Reston strains of bona fide Ebola, were distinguished principally by TAM expression. Lines with high levels of Axl and/or Tyro3 were more readily infected than TAM-negative cells. Introduction of either Tyro3 or Axl into filovirus-resistant cells rendered these cells susceptible to infection, and anti-Axl antibodies antagonized infection of Axl-expressing cells with MLV viruses pseudotyped with Ebola glycoprotein (Shimojima et al. 2006).

Similar results have been obtained using infection of endothelial cells with lentiviral vectors pseudotyped with Sindbis virus glycoproteins (Morizono et al. 2011). These experiments

also identified Gas6 and Pros1 as "bridging factors" that link PtdSer on the external surface of the viral envelope to Axl on the target cell. Depending on culture conditions, introduction of TAM cDNAs potentiated virus titers in infection-resistant cell lines $\geq$50-fold. This has also recently been observed for infection by the Dengue (DENV) and West Nile viruses (WNV) of the flavivirus family (Meertens et al. 2012). An unbiased cDNA transfection screen in human 293T cells, which are resistant to infection by these viruses, identified Tyro3 and Axl as factors that greatly enhance infection. Consistent with the interaction model depicted in Figure 1, this enhancement was found to be entirely dependent on the presence of a TAM ligand and also on the expression of PtdSer on the extracellular leaflet of the virus envelope (Meertens et al. 2012). In general, the above findings have been interpreted to suggest that TAM receptors serve as docking sites for TAM-ligand-bound virus particles. However, mutational analyses also indicate that tyrosine kinase activity is required for Axl potentiation of infection by Ebola (Shimojima et al. 2007) and DENV (Meertens et al. 2012), and thus active TAM signaling appears to be required for the potentiation of virus infection just as it is required for the phagocytosis of ACs. Given that (1) Axl activation potently suppresses type I IFN signaling in DCs and macrophages (Sharif et al. 2006; Rothlin et al. 2007; Shao et al. 2010), (2) type I IFNs are strong antiviral agents (Diamond 2003), and (3) suppression of type I IFN signaling is a mechanism that viruses exploit repeatedly as a means of immune evasion (Diamond 2003; Bonjardim et al. 2009; Versteeg and Garcia-Sastre 2010), the activation of TAM receptor signaling by viruses may prove to be an exceptionally effective mechanism of viral infection.

TAM RECEPTORS AND CANCER

There is a long association of TAM receptors with cancer—the first cDNAs for Axl and Mer were cloned from myeloid leukemia and lymphoblastoid lines, respectively (O'Bryan et al. 1991; Graham et al. 1994), and a truncated form of Mer (designated v-eyk) was identified initially as an avian retroviral oncogene (Jia et al. 1992; Jia and Hanafusa 1994). Axl was named from the Greek *anexelekto*, meaning "uncontrolled." Over the ensuing two decades, hundreds of papers have appeared that link TAM receptor and ligand expression to various forms of cancer (Linger et al. 2008; Verma et al. 2011). In general, these studies have reported overexpression or up-regulation of Axl, Mer, Tyro3, and/or Gas6. In many settings, however, a definitive demonstration that overexpression is causal for particular features of cancer development or progression has not been made. Elevated expression of TAM signaling components has been reported for leukemias (Graham et al. 1994, 2006; Hong et al. 2008), gliomas (Hutterer et al. 2008; Keating et al. 2010), colorectal carcinomas (Craven et al. 1995), breast cancers (Berclaz et al. 2001; Gjerdrum et al. 2010), gastrointestinal stromal tumors (Mahadevan et al. 2007), hepatocellular carcinoma (He et al. 2010), melanoma (Quong et al. 1994; Koorstra et al. 2009; Zhu et al. 2009), pancreatic adenocarcinoma (Song et al. 2010), and prostate cancer (Wu et al. 2004; Sainaghi et al. 2005), among several others.

Expression of Axl is correlated with an adverse prognosis in acute myeloid leukemia (Rochlitz et al. 1999), glioblastoma multiforme (Hutterer et al. 2008), pancreatic cancer (Koorstra et al. 2009), and esophageal adenocarcinoma (Hector et al. 2010). Axl up-regulation and activation have also been found to be a clinically significant feature of resistance to EGF receptor inhibitor and PI3K inhibitor therapies for non-small-cell lung cancer (Zhang et al. 2012; Byers et al. 2013). In many settings, Axl and/or Gas6 expression is most prominently associated with tumor metastasis, rather than growth of the primary tumor (Gjerdrum et al. 2010; Song et al. 2010). Consistent with this association, a small-molecule inhibitor of the Axl tyrosine kinase has shown efficacy primarily with respect to a reduced metastatic burden, rather than primary tumor growth, in mouse models of breast cancer metastasis (Holland et al. 2010). The link between TAM receptor expression and tumor metastasis is interesting in light of the importance of Axl and Tyro3 in the migration of

gonadotropin-releasing hormone (GnRH) neurons from the olfactory placode to hypothalamus of the brain (Allen et al. 2002a; Pierce et al. 2008). This migration of GnRH neurons involves Gas6 activation of the same downstream signaling pathways—PI3 kinase, ERK1/2, and Rac via Ras (Allen et al. 2002a,b; Nielsen-Preiss et al. 2007)—that are engaged downstream from TAMs in tumor cells.

TAM REGULATION OF THE VASCULATURE SYSTEM

TAM signaling plays an important role in the homeostatic regulation of blood vessel integrity and permeability. The TAM ligands Gas6 and Pros1 were first identified in and purified from aortic endothelial cells (Stitt et al. 1995), and studies using conditional Pros1 knockouts have shown that vascular endothelial cells are a major source of the Pros1 that appears in the circulation (Burstyn-Cohen et al. 2009). Axl and Tyro3 are also expressed by the vascular smooth muscle cells that surround these endothelia, and Gas6 and Pros1 have potent trophic effects on these cells, both in vitro and in vivo (Gasic et al. 1992; Fridell et al. 1998; Melaragno et al. 1999; Collett et al. 2007; Son et al. 2007; Cavet et al. 2008). The PI3 kinase/Akt pathway is again implicated as a key effector of TAM signaling in smooth muscle.

Damage to blood vessels results in the upregulation of both Axl and Gas6 (Melaragno et al. 1998), and a complex pattern of differential regulation of Axl, Mer, Gas6, and Pros1 has been reported in human atherosclerotic plaques (Hurtado et al. 2011). Defects in the clearance of apoptotic cells from these plaques are linked to progression of advanced atherosclerotic lesions, and the role of compromised TAM signaling in cardiovascular disease is a subject of active study (Ait-Oufella et al. 2008; Thorp 2010). *Pros1*$^{+/-}$ mice with a 50% reduction in Pros1 display vessel breaches, with leakage of blood into the parenchyma of tissues (Burstyn-Cohen et al. 2009). Pros1 has also been linked to vascular integrity in the brain. Pros1, signaling through Tyro3, has been implicated in maintenance of the blood–brain barrier and has been found to ameliorate hypoxic/ischemic blood–brain barrier disruption (Zhu et al. 2010).

In addition to these direct activities, TAM signaling has been shown to affect vascular integrity indirectly, through the regulation of platelet function. Loss of one or more TAM receptors has been observed to impair stabilization of platelet aggregates, at least in part by reducing platelet granule secretion. Gas6 activates PI3K/Akt signaling in platelets and stimulates tyrosine phosphorylation of β3 integrin, thereby amplifying thrombus formation (Angelillo-Scherrer et al. 2001, 2005).

PROSPECTS

In addition to the biological settings outlined above, there is a significant body of literature to suggest that TAM signaling may play regulatory roles in the nervous system. Microglia, the tissue macrophages of the brain, also express Axl and Mer (Gautier et al. 2012), and there is evidence that TAM signaling through these receptors controls the phagocytosis of ACs and the inhibition of inflammation in the CNS just as it does in macrophages and DCs in the periphery (Grommes et al. 2008; Weinger et al. 2011). Tyro3 is also prominently expressed by many CNS neurons (Lai and Lemke 1991; Lai et al. 1994; Prieto et al. 2000, 2007). Its role in these neurons has for the most part remained obscure, however, and therefore this area is wide open for future study.

As noted at the outset, TAM receptor and ligand functions are, in the main, devoted to the homeostatic regulation of phenomena that are regular, cyclic, and circadian. These signaling proteins operate in adult, fully differentiated tissues that are subject to constant challenge and regular renewal. These features, together with the fact that the TAMs are RTKs expressed on the cell surface, make the TAM system a particularly favorable target for therapeutic intervention.

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