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THE CONTRIBUTION OF TYRO3 FAMILY RECEPTOR TYROSINE KINASES TO THE HETEROGENEITY OF APOPTOTIC CELL UPTAKE BY MONONUCLEAR PHAGOCYTES

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Abstract

Mononuclear phagocytes comprise a mobile, broadly dispersed and highly adaptable system that lies at the very epicenter of host defense against pathogens and the interplay of the innate and adaptive arms of immunity. Understanding the molecular mechanisms that control the response of mononuclear phagocytes to apoptotic cells and the anti-inflammatory consequences of that response is an important goal with implications for multiple areas of biomedical sciences. This review details current understanding of the heterogeneity of apoptotic cell uptake by different members of the mononuclear phagocyte family in humans and mice. It also recounts the unique role of the Tyro3 family of receptor tyrosine kinases, best characterized for Mertk, in the signal transduction leading both to apoptotic cell ingestion and the anti-inflammatory effects that result.

Keywords

Apoptosis; Dendritic cells; Innate Immunity; Macrophages; Phagocytosis; Receptor Tyrosine Kinase; Review, tutorial

2. INTRODUCTION - THE IMPORTANCE OF MONONUCLEAR PHAGOCYTE UPTAKE OF APOPTOTIC CELLS

Clearance of apoptotic cells is important during embryonic development and in the maintenance of immunological self-tolerance [1], but becomes crucial during the resolution of infection [2-5]. During successfully controlled infections, large numbers of leukocytes die by apoptosis [6-8], and their prompt, efficient clearance by tissue macrophages safely disposes of the proteolytic enzymes that they contain. Tissue repair is hastened by mediators released by macrophages during apoptotic cell ingestion [9-13], which include transforming growth factor-β (TGF-β), platelet activating factor (PAF), prostaglandin E2 (PGE_2) and interleukin (IL-)10 [14-17]. In a contact-dependent fashion that is incompletely understood, macrophage recognition of apoptotic cells also suppresses production of inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), granulocyte-macrophage colony stimulating

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factor, IL-1β, IL-12 and IL-18 [18-23]. However, these same anti-inflammatory mediators released during apoptotic cell ingestion by macrophages have properties that can compromise host defenses against pathogens and promote fibrosis [24, 25]. By contrast, if apoptotic cells are not promptly ingested, they progress to a late apoptotic stage that is similar to necrosis, lose membrane integrity, and disintegrate [26]. Necrotic cells and late apoptotic cells drive maturation of immature dendritic cells and hence T cell activation [27-29]. Inflammation can be perpetuated when fragments of late apoptotic cells, notably those containing High Mobility Group Box-1 protein, bind to Toll-like receptor-4 (TLR4), better known as the receptor for purified lipopolysaccharide (LPS), thereby activating NF-κB [9, 30]. Uningested late apoptotic cells also release nucleosomes, which are formed *in vivo* exclusively by chromatin digestion during apoptosis. Nucleosomes are a major immunogen for autoantibodies in systemic lupus erythematosus [31-35] and are implicated in atherogenesis [36-38]. Thus, efficient apoptotic cell clearance contributes centrally to protective adaptive immunity, appropriate resolution of innate inflammation, and the prevention of autoimmunity.

Macrophage-independent mechanisms for apoptotic cell clearance exist [39-42]. Epithelial cells in the thymus and in the involuting female breast avidly ingest cells undergoing apoptosis in their respective organs [43-46]. Lung epithelial cells and fibroblasts ingest apoptotic cells *in vitro* (albeit less efficiently than do macrophages) [47-49]. Although the overall importance of apoptotic cell uptake by these cell types *in vivo* is unproven, it is plausible that they contribute significantly in the absence of overt inflammation. However, during steady state in most organs, and certainly during inflammation, mononuclear phagocytes are believed to clear most apoptotic cells. These considerations imply that understanding the molecular mechanisms controlling the response of mononuclear phagocytes to apoptotic cells and its consequences is an important goal with implications for multiple areas of biomedical sciences.

This review details the current understanding of heterogeneity of apoptotic cell uptake by different members of the mononuclear phagocyte family, and the central role in that process of one family of receptor tyrosine kinases (RTKs), the Tyro3 family. Because portions of this subject have been reviewed previously [50-53], emphasis will be on recent developments and their potential implications for human health and disease, and on unresolved questions. We also discuss why Tyro3 RTKs are so crucial for the signal transduction leading both to ingestion and to the anti-inflammatory effects that result.

3. HETEROGENEITY OF APOPTOTIC CELL UPTAKE BY MONONUCLEAR PHAGOCYTES

Mononuclear phagocytes are a heterogeneous group of hematopoietic cells that inhabit every organ [54-56]. In the most general of terms, the mononuclear phagocyte system consists of circulating monocytes, tissue macrophages and dendritic cells. Except for the plasmacytoid dendritic cell subset, all appear to derive from a common precursor [57, 58].

3.1. Monocytes

Monocytes begin their journey by emigrating from the bone marrow into the blood in a fashion that depends on CC chemokine receptor 2 (CCR2) under both normal and inflammatory conditions [59, 60]. CCR2 binds several CC chemokines, include CCL2 (formerly known as MCP- 1), a chemokine that specifically induces monocyte chemotaxis. Monocytes circulate briefly before migrating to tissues where they differentiate into macrophages or dendritic cells [61]. Some controversy persists regarding the potential of individual monocytes to differentiate into these two differentiated mononuclear phagocyte types; this controversy relates to the issue of monocytes subsets.

There is a long history of attempting to subdivide monocytes into subsets that possess different capacities for migration and subsequent differentiation. Human monocytes comprise two principal subsets, a majority "classical" $CD14^{high}$ CD16- population and a "non-classical" or "proinflammatory" $CD14^{low}$ CD16+ population [55, 62, 63]; a third, very minor double-positive subset has also been identified [64]. The CD16- subset, but not the CD16+ subset of human monocytes can differentiate *in vitro* into osteoclasts [65]. In a model of reverse-transendothelial migration [66], the monocytes that developed characteristics of dendritic cells were predominately CD16+ [67]. However, both subsets of human monocyte could differentiate into dendritic cells in culture when stimulated by cytokines [68]. The degree to which each of these monocyte subsets gives rise to other specialized mononuclear phagocyte cell types in non-lymphoid tissue is incompletely characterized.

Evidence from a transgenic model system suggests that circulating monocytes in mice also comprise two distinct phenotypes. These phenotypes can be distinguished based on their expression of two surface molecules, the CX3C chemokine receptor CX3CR1, which is the unique receptor for the chemokine CX3CL1 (fractalkine), and the Gr-1 epitope found on the Ly-6C/G family of glycosylphosphatidylinositol-linked molecules on myeloid cells. These two monocyte phenotypes are, respectively, a short-lived $CX3CR1^{low}$ $CCR2^{+}$ $Gr\text{-}1^{high}$ subset that can be recruited to sites of inflammation, and a longer-lived $CX3CR1^{high}$ $CCR2^{-}$ $Gr\text{-}1^{low}$ "resident subset" that constitutively migrates to a variety of tissues in a CX3CR1-dependent fashion [69]. The $CX3CR1^{high}$ monocyte subset was recently shown to crawl along vascular endothelia in a fashion that depends on LFA-1 (CD11a/CD18), permitting them very rapid entry into sites of inflammation [70]. Importantly, CX3CR1 expression also distinguishes the two main subsets of monocytes in the rat [71], and in humans, where the $CD14^{low}$ $CD16^{+}$ population expresses higher levels [69]. Thus, an emerging paradigm holds that mammalian monocytes can be divided into separate lineages distinguishable by their level of expression of CX3CR1.

Sunderkotter et al. modified this concept somewhat [72], in a study that analyzed murine monocytes using the ER-MP20 monoclonal antibody, which specifically recognizes only Ly-6C, a macrophage-specific protein, and not Ly-6G, which is also expressed by other myeloid cells. Because the previous study by Geissman et al. [69] had defined Gr-1 expression using the monoclonal antibody RB6-8C5, which recognizes an epitope common to Ly-6G and Ly-6C [73], direct comparison between the two studies is difficult. Sunderkotter et al. showed that $Ly\text{-}6C^{high}$ monocytes were recent bone marrow emigrants, which could be

recruited to sites of inflammation, and that they gave rise to the more mature Ly-6C^{low} monocytes, which had lost this ability [72]. The Ly-6C^{low} subset also preferentially expressed CD11c and the anti-adhesive molecule CD43. They further showed a continuum of Ly-6C expression between Ly-6C^{high} and Ly-6C^{low} subsets, with a transient Ly-6C^{intermediate} population. These data imply a developmental rather than parallel lineage relationship between the two monocyte phenotypes. In other studies, both the Gr-1^{high} (Ly-6C/G^{high}) and the Gr-1^{low} murine monocyte subsets were originally reported to be able to differentiate into dendritic cells *in vivo*, but their ability to differentiate into macrophages *in vivo* was unknown. A later study focusing on the pulmonary mononuclear phagocyte system confirmed that both monocyte subsets could differentiate into lung dendritic cells, but that only Gr-1^{low} monocytes had the potential to differentiate immediately into lung macrophages [74].

The ability to ingest apoptotic cells is gained as monocytes differentiate within tissues. Monocytes freshly isolated from the human peripheral blood have very limited capacity to ingest apoptotic cells [75, 76]. Incubation in serum or in TGF-β induces some ability for human monocytes to ingest apoptotic cells, generally with a marked dependence on CD36 and vitronectin [77]. Because differentiation of monocytes into the wide variety of macrophages and dendritic cells found in individual organs appears to be under complex and likely unique regulation, these seminal data will need re-examination as the conditions for organ-specific differentiation are defined. Like most other aspects of monocyte biology in the mouse, the capacity of murine peripheral blood monocytes to ingest apoptotic cells is largely unknown, due to the difficulty in isolating sufficient numbers of this cell type at high purity. To investigate whether monocytes newly recruited to a site of inflammation contribute to apoptotic cell clearance, we used in situ vital-staining of resident tissue macrophages in a well-characterized model of CD4 T cell– dependent lung inflammation [78]. Compared to resident alveolar macrophages, monocytes recruited to the lung ingested apoptotic cells poorly, whereas they avidly ingested immunoglobulin-opsonized particles. In this antigen-driven, non-infectious model system, overall numbers of resident alveolar macrophages did not change significantly over the course of the response and the majority of recruited monocytes did not become long-term residents. By contrast, in LPS-induced lung inflammation, Maus et al. found high alveolar macrophage turnover and persistent replacement by immigrating monocytes [79]. These differences in results likely relate to the degree to which the inflammatory process induces apoptosis of resident tissue macrophages, a characteristic feature of some infections [80-88]

3.2. Resident tissue macrophages

The phenotype of resident macrophages in different organs obviously differs very markedly, spanning the range from hepatic Kuppfer cells to microglial cells of the central nervous system. Resident tissue macrophages derive ultimately from hematopoietic precursors, but there is evidence that in the absence of inflammation in some organs, their numbers are sustained primarily by local proliferation [89-92]. In the mouse, the resident peritoneal macrophage is often taken to be the “generic” macrophage, due to the ease of its isolation. Peritoneal macrophages bind apoptotic cells readily by means of multiple receptors and ingest apoptotic cells fairly avidly, making them an ideal reference cell type. In peritoneal

macrophages and likely in most mononuclear phagocyte cell types, a crucial signal for ingestion is stereospecific recognition of externalized phosphatidylserine (PS) on the apoptotic cell surface [93, 94] via one or more receptors that are blocked, in mice, by monoclonal antibody 217 [95]. The biochemical nature of stereospecific PS recognition remains elusive [96].

Other than the peritoneal macrophage, the most thoroughly studied resident macrophage is probably the alveolar macrophage, the principal resident phagocyte of the lungs. Resident alveolar macrophages show markedly reduced apoptotic cell uptake *in vitro* relative to resident peritoneal macrophages (in the mouse) [97, 98] or relative to alveolar macrophages harvested from rabbits three days after the induction of immune-complex-induced injury [75]. The reduced phagocytosis in alveolar macrophages was attributable in part to decreased adhesion of the apoptotic cells [98], as well as to markedly decreased expression of protein kinase C (PKC) βII, the sole isoform of PKC required for apoptotic cell uptake [99]. Although the pulmonary collectin surfactant protein A increased apoptotic cell ingestion by alveolar macrophages [100, 101], the effect was minor and did not increase ingestion by alveolar macrophages to the levels seen using peritoneal macrophages [98]. Human resident alveolar macrophages also show low capacity to ingest apoptotic cells [102-105]. Interestingly, resident human alveolar macrophages also have very decreased expression of PKC βII, relative to monocytes [106].

Some data on this issue also exist for microglia, the resident mononuclear phagocyte of the central nervous system. Microglial cells from surgically resected normal human or rat brains ingested autologous apoptotic cells, which they bound using CD36 and recognize via externalized PS [3, 107, 108]. Little is currently known about apoptotic cell uptake by resident macrophages in other tissues, especially for humans.

Mature tissue macrophages can also assume a variety of activation states that have been characterized as classical activation in response to interferon-gamma, and alternative activation (reviewed in [109, 110]). The capacities of macrophages in these different activation states to ingest apoptotic cells has received only scant attention [111]. Polarized macrophages (induced *in vitro* from human peripheral blood CD14+ monocytes supplemented with Granulocyte-Colony Stimulating Factor) showed increased ability to bind and ingest apoptotic cells, and unique ability to ingest cells in the early stages of apoptosis [112]. Additional studies examining this issue via polarization of resident tissue macrophages from various organs would contribute to the understanding of specific disease states.

3.3. Dendritic cells

Dendritic cells are a heterogeneous population of antigen-presenting cells with complex ontogeny, but distinct dendritic cells subsets can be identified based upon anatomic location, migratory pathways, and specific immunological function [113]. In the resting state, two major dendritic cells lineages can be distinguished: conventional dendritic cells and plasmacytoid dendritic cells. Conventional dendritic cells were previously called myeloid dendritic cells, a term that is falling from usage since it was found that conventional dendritic cells can develop from both myeloid and lymphoid precursors [114].

Conventional dendritic cells display a characteristic stellate morphology and participate in classical dendritic cell functions including uptake, processing, and presentation of antigens to naïve and memory T cells. Shortman and Naik divide conventional dendritic cells into "lymphoid-tissue-resident" and "migratory" populations [113]. Lymphoid-tissue-resident conventional dendritic cells include three subsets within the spleen or lymph nodes (CD4+/CD8−, CD4−/CD8+, and CD4-/CD8-) and up to four additional conventional dendritic cells populations in the thymus. Migratory dendritic cells include epidermal Langerhans cells [115] and the interstitial dendritic cells of non-lymphoid organs, including the dermis, liver, and the intestinal, respiratory and reproductive tracts. In response to inflammatory stimuli, migratory conventional dendritic cells travel in a CCR7-dependent manner to draining lymph nodes, where they present antigen to naïve T cells.

Whilst migratory conventional dendritic cells are exiting peripheral tissues during inflammation, in the mouse they are replaced by inflammatory dendritic cells that are derived from $CX3CR1^{lo}$ $CCR2^{+}$ $Gr\text{-}1^{+}$ inflammatory monocytes (as described above) and possibly from CD11c+ dendritic cell precursors in the blood. Gene-targeting has confirmed the essential role of the chemokine receptor CCR2 in the recruitment of inflammatory dendritic cells to the skin, spleen and lungs [116-118]. Inflammatory dendritic cells resemble resting migratory conventional dendritic cells in phenotype, although it is uncertain whether they also migrate to regional nodes to sustain antigen presentation, or are predominately active within the inflamed tissues. The latter possibility is supported by experiments in mice showing dendritic cell-dependent local production of TNF-α and inducible nitric oxide synthase in response to *Listeria monocytogenes* [59] and by promotion of tissue-specific T_H1 polarization by IL-12 production in response to *Cryptococcus neoformans* (Osterholzer et al., manuscript submitted).

The efficiency and functional consequence of the uptake of apoptotic cells by conventional dendritic cells depends not only on the dendritic cells subset, but also on the micro-anatomic location and context in which the apoptotic cell is encountered (i.e., resting vs. inflammatory conditions) [119]. Uptake of apoptotic cells within lymphoid structures (including lymph nodes and the thymus) and by immature migratory conventional dendritic cells without simultaneous stimulation via pathogen recognition receptors is believed to contribute crucially to maintenance of T-cell tolerance [120-126]. This concept has been challenged recently by the finding that apoptotic cells derived from polyclonally-activated peripheral blood mononuclear cells (PBMC), but not those from resting PBMC, could induce maturation of human monocyte-derived dendritic cells [127]. In contrast, uptake of a late apoptotic cell (or necrotic cell) induces conventional dendritic cells to mature [122, 128], to migrate to local lymph nodes (for migratory dendritic cells), and to stimulate T cell activation. Although this process may enhance host defense against microbial antigens, it also risks presentation of self antigens to T cells in a stimulatory context and the subsequent generation of autoimmunity.

Plasmacytoid dendritic cells comprise an independent dendritic cell lineage [129-131]. Formed primarily in the bone marrow, these dendritic cells take up residence in both lymphoid and non-lymphoid organs. They produce large amounts of type-1 interferon in response to a variety of microbial stimuli and are, therefore, particularly important to anti-viral immunity

(although conventional dendritic cells also may serve a role). Whether plasmacytoid dendritic cells participate in the clearance of apoptotic cells has not been established. Dalgaard et al. compared the ability of myeloid dendritic cells and plasmacytoid dendritic cells to ingest apoptotic leukemic cells and concluded that plasmacytoid dendritic cells do not contribute to apoptotic cell uptake [132]. However, Hoeffel et al. demonstrated that plasmacytoid dendritic cells acquisition of antigens from cells undergoing viral-induced apoptosis promoted cross presentation to CD8+ T cells [133]. Whether these were late apoptotic cells (and thus more stimulatory than the leukemic apoptotic cells studied by Dalgaard et al.) cannot be determined.

4. THE TYRO3 FAMILY OF RTKs

The mammalian Tyro3 family consists of three closely related receptor tyrosine kinases (RTKs) that are involved in apoptotic cell uptake and immunomodulation. The three individual family members have acquired a variety of names, reflecting their initial independent identification by multiple laboratories. Table 1 lists the names used in this review (Tyro3, Axl and Mertk), together with common synonyms and identifiers for the human and murine genes. Variable amounts of all three RTKs are expressed by normal and malignant cells of neural, lymphoid vascular and reproductive origin [134]. Tyro3 family members were originally identified for their transforming ability when over-expressed [135-139], and as such, can be considered protooncogenes. Indeed, this concept has been supported by over-expression in both murine and human systems, and several human cancers over-express Mertk (summarized in [140]). All three RTKs are involved in megakaryocytopoiesis and platelet aggregation [140-142]. Because blockade of Tyro3 RTKs inhibits thrombosis without enhancing bleeding, this activity is under intense scrutiny from the pharmaceutical industry. Axl is also implicated in natural killer cell differentiation and vascular remodeling [143]. It is likely that the complete range of properties of this interesting molecular family remains undefined.

4.1. Structure & function of Tyro3 RTKs

Tyro3 family RTKs are defined by a unique shared sequence (in single letter amino acid code, KWIAIES) within their kinase domain. Tyro3 is prominently expressed in the developing brain, as well as in adult kidney, testis and ovary, and by both human pulmonary artery endothelial cells and osteoclasts. Axl appears to be the most widely distributed member of the family, due to its expression in cell lines of epithelial, mesenchymal and hematopoietic origins as well as non-transformed cells [135]. Mertk was originally named c-mer due to its expression in monocytes, epithelial cells, and reproductive tissue [144].

Tyro3 RTKs are single-pass type 1 transmembrane proteins with characteristic extra- and intracellular modular structures. All three appear to be heavily glycosylated; Mertk has 13 potential N-linked glycosylation sites. The extracellular region of each RTK includes two amino terminal immunoglobulin motifs followed by two more membrane proximal fibronectin type-III motifs. Immediately after molecular cloning of these RTKs, it was suggested that these motifs might participate in cell-cell or cell-matrix interactions [137]. Axl was shown to mediate homophilic binding leading to cell aggregation when over-expressed in S2 cells [145], but to date, there is no direct in vivo experimental evidence for this attractive

possibility. The alternative possibility, that these motifs contribute to binding of Tyro3 RTKs in cis to other macrophage cell surface receptors, is supported by evidence for a pairing of Axl (but not Tyro3 or Mertk) with the IL-15Rα chain [146]. This interaction required the extracellular portion of Axl and was present in the absence of ligand stimulation. Treatment with IL-15 induced tyrosine phosphorylation of both Axl and IL-15Rα , and activation of the phosphatidylinositol-3 kinase (PI-3K)-Akt pathway, indicative of the functional nature of this heterologous receptor pairing. These data illustrate the capacity of Tyro3 RTKs to serve as signaling molecules in association with other receptors, a possibility to which we will return.

All three Tyro3 family RTKs are receptors for the serum protein growth arrest-specific gene 6 (Gas6), whereas only Tyro3 binds protein S. Both Gas6 and protein S are vitamin K-dependent soluble factors that can bind externalized PS [147-149], the hallmark of an apoptotic cell. Binding of these soluble factors provides a means by which Tyro3 family RTKs could contribute to apoptotic cell recognition. However, Biacore assay has shown that the association of Mertk with Gas6 is of lower avidity than that of Axl and Tyro3 [147]. This finding suggests that Mertk may depend to a greater degree than other family members on association with other apoptotic cell-binding receptors to initiate apoptotic cell ingestion. One way in which this could occur is via heterodimerization of Mertk with other Tyro3 RTKs, as has recently been suggested [150]. The spatial relationships of Axl binding to Gas6 was recently clarified by analysis of crystal structure at 3.3Å resolution of a minimal human Gas6-Axl complex. Results revealed an assembly of 2:2 stoichiometry, in which the two immunoglobulin-like domains of Axl were cross-linked by the first laminin G-like domain of Gas6, without direct Axl-Axl or Gas6-Gas6 contacts. This study also found major and minor Gas6 binding sites on Axl, and showed that both binding sites were required for productive transmembrane signaling. Interestingly, only the minor Gas6 binding site is highly conserved in Tyro3 and Mertk [151].

The complexity of ligand-binding by Tyro3 RTKs is increased by the finding that soluble Axl can be generated by ADAM10-dependent cleavage, and is found in high concentration in mouse serum in association with Gas6 [152]. Although no such soluble forms of murine Tyro3 or Mertk were detected in that study, a soluble form of human Mertk was predicted based on an alternatively spliced RNA transcript [137]. Soluble Mertk was recently found to be produced by multiple human macrophage cell types, and to inhibit both macrophage clearance of apoptotic cells and platelet aggregation [140].

4.2. Difference in Tyro3 RTK expression among mononuclear phagocyte subsets

Tyro3 family RTKs were first suspected to contribute to apoptotic cell clearance based on observations in two separate systems: gene-targeted mice lacking expression of all three RTKs, which showed blindness and massive apoptotic cell accumulation in the spleen [134]; and positional cloning of a gene involved in retinitis pigmentosa in rats [153, 154], which identified a spontaneous mutation in Mertk. Blindness in the rats proved to result from defective ingestion of photoreceptor outer segments by retinal pigment epithelial cells, a process closely akin to apoptotic cell uptake [155]. The central role of these RTKs in apoptotic cell uptake was thereafter rapidly and conclusively confirmed using the gene-targeted mice.

Triple knockout mice lacking all three Tyro3 RTKs developed a severe lymphoproliferative disorder characterized by auto-immunity and widespread thrombosis associated with anti-phospholipid antibodies [156]. Mice lacking Mertk expression showed accumulation of uningested apoptotic thymocytes after injection of dexamethasone, and reduced clearance of labeled apoptotic cells from the spleen and thioglycollate-treated peritoneal cavity, following intravenous and intraperitoneal injection, respectively [157].

Of the three Tyro3 RTKs, monocytes appear to express mRNA only for Mertk, the family member most restricted to the mononuclear phagocyte lineage [137, 138]. Using flow cytometry, we found that mononuclear phagocytes freshly-recruited to the lungs express only very low amounts of Mertk [78]. This observation, in agreement with unpublished data from Behrens et al. [158], is not necessarily at odds with the original finding that Mertk could be detected on circulating human monocytes, as that earlier data relied on RT-PCR [137].

Tissue resident macrophages may differ in expression of individual Tyro3 RTKs {e.g., resident murine alveolar macrophages appear to express all three receptors, whereas resident peritoneal macrophages from unstimulated mice express only MerTK (unpublished observation)}, although this subject has not been defined for many organs in either mice or humans. In the primary tissue macrophages for which it has been examined, dependence on Mertk for apoptotic cell uptake is significant [78, 98, 157], whereas the role for Tyro3 and Axl appears more minor [150]. To our knowledge, expression of Tyro3 RTKs and their contribution to apoptotic cell uptake have not been examined in relation to polarized states of macrophage activation in either species.

The role of Tyro3 RTKs in apoptotic cell uptake by murine dendritic cells has been investigated by two groups. Behrens et al. found that splenic dendritic cells of both conventional (CD11c+, CD11b+) and CD8αα+ subsets expressed Mertk, whereas the absence of Mertk+ cells in B cell zones of the spleen argued against expression by follicular dendritic cells [158]. In that study, bone marrow-derived dendritic cells from Mertk-deficient mice showed no impairment in uptake of apoptotic cells. Similarly, Mertk was shown by Seitz et al. to be unnecessary for apoptotic cell uptake by bone marrow-derived dendritic cells and splenic dendritic cells. By contrast, they found reduced apoptotic cell ingestion by bone marrow-derived dendritic cells, splenic dendritic cells, and to a lesser degree thioglycollate-elicited peritoneal exudate macrophages from mice lacking either Axl, Tyro3 or both RTKs [150]. There are currently no data on this subject in humans or in resident dendritic cells from mucosal surfaces in mice.

The differential capacity of tissue macrophages versus dendritic cells to ingest apoptotic cells [50] has important consequences for immunoregulation. For example, because immature dendritic cells but not macrophages can induce a specific cytotoxic T cell response after ingesting virally-infected apoptotic cells [120], development of specific anti-viral immunity depends on the cell type of the mononuclear phagocyte that ingests the infected apoptotic cells.

5. TYRO3 RTKS AS SIGNAL-TRANSDUCING ELEMENTS DURING APOPTOTIC CELL UPTAKE

5.1. Basics of signal-transduction during apoptotic cell uptake

Apoptotic cell recognition by mononuclear phagocytes activates an intracellular signaling cascade leading to efficient apoptotic cell engulfment. This engulfment process was originally believed to be similar to phagocytosis triggered by Fc receptors (FcR), and the two processes do share some characteristics, such as dependence on PI-3K and phospholipase C γ (PLC γ) [159, 160]. However, both biochemical and morphological differences between uptake of the two types of particles are now appreciated. PKC βII is uniquely required for apoptotic cell ingestion [99], which differs from the PKC isoform requirements for macrophage phagocytosis of other particles [161, 162]. Apoptotic cell ingestion does not require the cytoplasmic tyrosine kinase Syk [163], which is essential for FcγR-mediated ingestion [164, 165]. FcR-mediated uptake involves "membrane zippering" [166], whereas apoptotic cell uptake has been show to involve macro-pinocytosis, leading to formation of spacious phagosomes [112, 167, 168] (although this point has been contested [169-171]). The unique features of the apoptotic cell engulfment process have earned it a new term, "efferocytosis" (from effero — to carry to the grave) [172].

Because absence or inhibition of Tyro3 RTKs has no effect on FcR-mediated phagocytosis, to understand their role in apoptotic cell clearance it is helpful to consider the minimal signaling pathways essential for that process, which are strictly conserved between worms (such as *Caenorhabdiis elegans*) and mammals **(Fig. 1)**. Genetic analysis in *C. elegans* [173] has identified two crucial epistatic pathways. One pathway consists of the cell surface receptor ced-1 (likely mammalian homolog: lipoprotein receptor-related protein, also known as CD91), the intracellular adapter ced-6 (GULP), and the ATP-binding cassette transporter ced-7 (mammalian homolog recently shown to be ABCA7 [174]). The other pathway consists of the adaptor protein ced-2 (mammalian homolog CrkII), the adaptor protein ced-5 (Dock180), the Rho family GTP-binding protein ced-10 (Rac1), and the Rho family GTP-binding protein ced-12 (ELMO) [175-177]. The ced-1, -6, -7 pathway also acts genetically upstream of ced-10 in worms [178], but the biochemical point of connection between the two pathways is not yet established.

The ced-2, -5, -10, -12 pathway (CrkII-Dock180-Rac-ELMO in mammals), which is entirely intracellular, is required for actin cytoskeleton restructuring during phagocytosis. This pathway is regulated by RhoG, which increases apoptotic cell engulfment, and RhoA, which decreases it [179]. In keeping with this finding, RhoG and its exchange factor TRIO were found to interact with ELMO, promoting Rac1 activation and cytoskeletal reorganization [180]. However, exactly how this intracellular pathway interacts with the many surface receptors involved in apoptotic cell engulfment remains incompletely defined. Until recently, the only known link was with the αvβ5 integrin, which must interact with the $p130^{Cas}$-CrkII-Dock180 complex for apoptotic cell internalization [181]. It was also known that inhibitors of protein tyrosine kinases blocked apoptotic cell uptake [159, 181] by both dendritic cells, which use αvβ5 integrin, and macrophages, which use αvβ3 integrin [121].

5.2. Features of Tyro3 RTKs that facilitate signal transduction

The properties of Tyro3 family members (reviewed in [53]) imply that they could interact with many other macrophage molecules to transduce signals during apoptotic cell ingestion. Besides their tyrosine kinase activity, such properties include their ability to serve as cell surface receptors for soluble PS-binding proteins, their multiple extracellular motifs reminiscent of adhesion molecules, and their intracellular multi-ligand domain. Such a signaling role is supported by several types of data.

First, prompt and specific tyrosine phosphorylation of Mertk itself is induced by exposure to apoptotic cells (for macrophages) or outer rod segments (for retinal pigment epithelial cells) [160, 182] . This finding matches the suspected mechanism of activation of most RTKs by ligand-induced oligomerization, typically dimerization. Oligomerization yields an active kinase via auto-transphosphorylation of tyrosines in the kinase activation loop or juxtamembrane region [183]. Indeed, a chimeric molecule containing the transmembrane and intracellular domains of Mertk showed ligand-inducible tyrosine autophosphorylation [184]. RTK tyrosine phosphorylation is also needed to form binding sites within the intracellular multi-ligand domain for SH2-domain containing proteins.

Second, the intracellular multi-ligand domain of Tyro3 family RTKS have been shown to bind many signaling intermediaries known or suspected to be involved for apoptotic cell engulfment. For example, interaction of Tyro3 with its ligand protein S recruits Src [185], and the p85 subunit of phosphatidylinositol-3-OH kinase (PI-3K) [186], which is required for apoptotic cell ingestion [159]. Axl can bind PI-3K, PLC γ, Grb2, Src, and others, presumably via their SH2 domains. Axl also binds C1-TEN (C1 domain-containing phosphatase and TENsin homologue), a protein without other currently identified partners [187, 188].

Third, dimerization of Mertk during apoptotic cell recognition leads to activation of downstream mediators. One example is the tyrosine phosphorylation of PLC γ [160], a key signaling event that leads to formation of inositol 1,4,5 trisphosphate and diacylglycerol, which are essential for cytoskeletal rearrangements. Similarly, ligand-dependent activation of Mertk on human monocytes induces phosphorylation and release from MerTK of the guanine exchange factor Vav1, and subsequent activation of the RhoA family members Rac1, Cdc42 and RhoA [189]. This constitutive, SH2-dependent, but phosphotyrosine-independent interaction between Mertk and Vav1 is unusual. The cytoplasmic domain of Mertk has also been shown to be able to tyrosine phosphorylate PI-3K, Shc and Grb2 [190]. It is likely that ligand-induced oligomerization occurs during apoptotic cell recognition by other Tyro3 family receptors, but there is also potential for ligand-independent dimerization [151, 191].

Mertk so far appears unique in its ability to alter the cytoskeleton on apoptotic cell binding through small G protein regulators of cytoskeletal dynamics such as Rac1, Cdc42 and RhoA [184]. The Birge laboratory has shown that Mertk activation (by Gas6 or via a constitutively active Mertk construct) induces Src-mediated phosphorylation of focal adhesion kinase (FAK), which in turn recruits FAK to the αvβ5 integrin. The ultimate result is Rac1 activation via the 130^{CAS}-CrkII-Dock180 complex [192]. This finding is important because it indicates involvement of Mertk in the classical apoptotic cell signaling pathway

(Fig. 1). Conversely, during ingestion of photoreceptor outer segment fragments by retinal pigment epithelial cells, phagocytosis and signaling involving MerTK were abolished by absence either of αvβ5 integrin or of the apoptotic cell-binding soluble factor milk fat globule-EGF-factor 8 (MFG-E8), which bind αvβ5 integrin but not Mertk [193]. Taken together, these findings imply that neither Mertk nor αvβ5 integrin can be considered simply to be downstream of the other. Instead, the two molecules appear to cooperate to mediate apoptotic cell recognition. It is likely that Mertk interacts with additional transmembrane molecules, e.g., we have recently found evidence that scavenger receptor A I/II (CD204) is essential for optimal activation of MerTK and subsequent signaling required for apoptotic cell ingestion by murine macrophages (Todt et al., submitted).

5.3. What's so special about Tyro3 RTKs?

A wide variety of macrophage surface receptors from unrelated molecular families have been implicated in apoptotic cell ingestion [10, 101, 194-203]. Why so many receptors are involved in this process is unresolved. One viewpoint holds that redundancy is essential to safeguard such a crucial process. This explanation is supported by macrophage recognition of ICAM-3 on apoptotic neutrophils but not lymphocytes [204, 205]. Alternatively, Gregory and Devitt have suggested that this redundancy increases the flexibility of the system, by allowing a more specific response to the context in which the apoptosis occurs [206]. Multiple low-affinity receptor-ligand interactions may jointly serve as a high avidity complex, similar to the immunological synapse formed between T cells and antigen-presenting cells.

A corollary of this viewpoint, that receptors from different molecular families could serve different and fundamentally unique functions, is particularly relevant to the Tyro3 RTKs. Among the bewildering array of receptors implicated in apoptotic cell uptake, the evidence for involvement of many comes only from antibody blocking experiments that did not distinguish between a role in apoptotic cell adhesion and a signaling role essential for ingestion [167]. Importantly, adhesion of apoptotic cells to a variety of murine tissue macrophages and macrophage cell lines is not inhibited by function-blocking monoclonal antibody against Mertk [98]; whether this is the case for Axl and Tyro3 in other mononuclear phagocyte subsets is unknown. Normal tethering of apoptotic cells is seen in macrophages and dendritic cells from Mertk deficient mice and in macrophages from transgenic mice lacking MFG-E8, both of which show highly defective in vivo apoptotic cell clearance [157, 207]. Further support for an essential signaling role for Tyro3 RTKs comes from the observation that an overt autoimmune phenotype results from deletion of only a subset of the many genes implicated in apoptotic cell clearance. Intriguingly, Tyro3 RTKs are among them [134, 208], along with MFG-E8 [209], serum amyloid P-component, C1q, C4 and IgM [176].

Tyro3 RTKs, especially Mertk, also appear to contribute to the immunosuppressive effect of apoptotic cell engagement. Mice lacking Mertk surface expression displayed hypersensitivity to LPS in vivo that could be largely reversed by anti-TNF-α. Relative to peritoneal exudate macrophages from wild-type mice, peritoneal exudate macrophages from these mutant mice over-produced TNF-α and showed increased and sustained binding of NF-kB to the TNF-α promoter [210]. Splenic dendritic cells from triple-mutant mice lacking

expression of all three Tyro3 RTKs exhibited markedly increased expression of major histocompatibility complex class II molecules and CD86 after *in vitro* LPS stimulation [156]. Mertk is also required for apoptotic cell-induced inhibition of NF-kB activation by LPS in murine bone marrow-derived dendritic cells [211]. Collectively, these findings could imply that signals emanating from Tyro3 RTKS (or possibly just Mertk) intersect signals arising from the TLR4/CD14 complex. This exciting possibility clearly merits additional study. Interestingly, Ebola and Marburg viruses use Tyro3 RTKs to gain cell entry [212], which has been suggested to contribute to the dysregulation of the immune system and vascular endothelium seen during infection with these highly pathogenic filoviruses.

A significant increase in the understanding of how Tyro3 RTKs contribute to the immunomodulatory effect of apoptotic cells came from the recent finding that activation of Axl by Gas6 or apoptotic cells induces Twist proteins 1 and 2 [213], which are basic helix-loop-helix transcriptional repressors that inhibit production of TNF-α and other NF-κB-dependent inflammatory cytokines [214]. In a separate study, the typical anti-inflammatory response in macrophages ingesting apoptotic cells was not seen when the target was itself a macrophage induced to apoptosis by free-cholesterol loading (but not by ultraviolet irradiation or exposure to oxidized low density lipoproteins) of elicited murine peritoneal macrophages [215]. In this case, there was induction of TNF-α and IL-6 that was reduced in the absence of Mertk, but not of CD91, another receptor implicated in apoptotic cell uptake. Inflammatory cytokine release required cell-cell contact and the ERK 1/2 signaling pathway, but neither apoptotic cell ingestion nor the TLR adapter MyD88. These findings implicate Mertk as a potential therapeutic target in late in atherosclerotic plaques.

6. CONCLUSIONS

Given the complex ontogeny of tissue macrophages and dendritic cells, it is simplistic to make broad generalizations about apoptotic cell uptake of these two cell types without reference to their source and its state of inflammation. The phenotype of tissue macrophages and dendritic cells residing in different organs has probably been selected during evolution to provide an optimal balance between the potentially immunosuppressive effects of apoptotic cell ingestion (relative to that organ's exposure to pathogens) and the potentially damaging effects of delayed apoptotic cell clearance. Differences in expression by mononuclear phagocytes of the Tyro3 RTKs, and possibly differences in the association of Tyro3 RTKs with other receptors, are undoubtedly a significant component of this evolutionary process. By contrast, monocytes recruited into these tissues appear to start out largely without ability to ingest apoptotic cells, and hence appear to be highly malleable by the environment to which they are recruited.

The essential role of Tyro3 family RTKs in apoptotic cell uptake by mononuclear phagocytes likely results because they can perform two crucial functions simultaneously: (a) providing assembly points for a broad range of signaling intermediaries; (b) activating multiple molecules crucial for actin cytoskeleton restructuring. Tyro3 RTKs probably also contribute to form the phagocyte:apoptotic cell synapse because they are cell surface receptors for soluble PS-binding proteins, and possibly because their extracellular motifs can interact with adhesion molecules on the apoptotic cell, or with other receptors on the

phagocyte surface. Because Tyro3 RTKs appear to be unique among receptors for apoptotic cells in displaying this range of contributions, we hazard the prediction that they will prove to be the central “trigger” through which the apoptotic cell ingestion process is initiated.

Until the factors controlling differentiation of specific macrophage and dendritic cell subsets from monocytes are better defined, results from analyses of mononuclear phagocyte cell lines and *in vitro*-manipulated monocytes must be validated against the actual behavior of macrophages and dendritic cells in different tissues and in various disease states. This validation process, far from being “descriptive”, is a crucial step in the translation of basic science into approaches that can be tested in clinical research. A robust molecular understanding of apoptotic cell clearance by specific subsets of mononuclear phagocytes holds great promise for novel therapeutic approaches to most chronic diseases.

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Abbreviations

FAK	focal adhesion kinase
FcR	Fc receptor(s)
Gas6	growth arrest-specific gene 6
IL-	interleukin
LPS	lipopolysaccharide
MFG-E8	milk fat globule-EGF-factor 8, also known as lactadherin
PAF	platelet activating factor
PBMC	peripheral blood mononuclear cells
PGE_2	prostaglandin E2
PKC	protein kinase C
PLC	phospholipase C
PS	phosphatidylserine
RTK	receptor tyrosine kinase
TGF-β	transforming growth factor-beta
TLR4	Toll-like receptor-4
TNF-α	tumor necrosis factor-alpha

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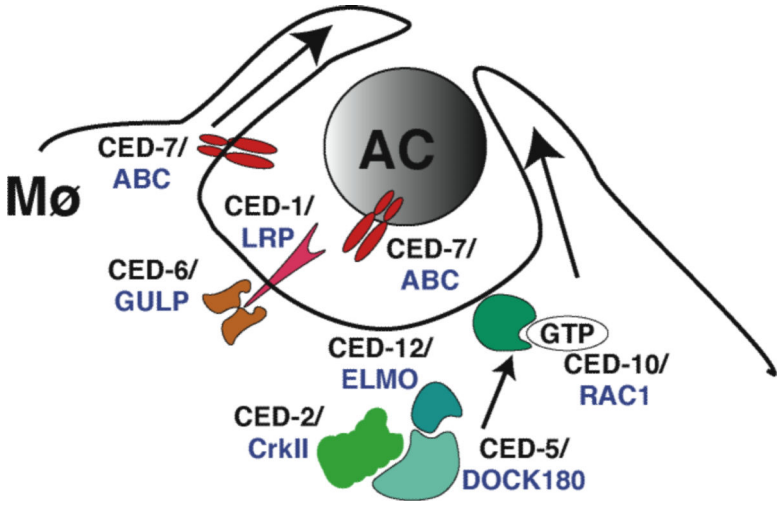

Figure 1. Schematic diagram of the epistatic pathways of essential genes for apoptotic cell clearance in worms, with presumed mammalian homologs

The engulfing cell (for *C. elegans*) or macrophage is shown in outline, and the apoptotic cell (AC) is in gray. The names of *C. elegans* genes are shown in black letters and those of the corresponding mammalian genes are in blue letters. The proteins of the CED-1/CED-6/CED-7 pathway are shown in red. Note that CED-7 must be present on both the apoptotic cell & the engulfing cell. The proteins of the CED-2/CED-5/CED-10/CED-12 pathway are in green. Arrows indicate actin cytoskeleton-driven membrane reorganization leading to engulfment. Adapted from [175]

Table 1

Names, synonyms & gene ID of Tyro3 RTKs

Name	Synonyms	GeneID[1]	OMIM[2]
Tyro3	Sky, Rse, Bit, DTK, Tif, Etk-2	7301 (h)	600341
		22174 (m)	
Axl	Ark, Ufo, Tyro7, AI323647	558 (h)	109135
		26362 (m)	
Mertk	Tyro12, c-mer, Eyk, Nyk, RP23-30M20.1	10461 (h)	604705
		17289 (m)	

[1](h) = human gene, (m) = murine gene, Entrez Gene Home (http://www.ncbi.nlm.nih.gov)

[2]OMIM, Online Mendelian Inheritance in Man

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