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Focus on Molecules: MERTK

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1. Structure

MERTK (UniProt accession Q12866) is a single pass transmembrane receptor that belongs to the TAM (Tyro3, Axl and Mertk) family of receptor tyrosine kinases. MERTK is highly expressed in monocytes/macrophages, testis and epithelial cells including the retinal pigment epithelium (RPE) (Fig. 1A). The human *MERTK* gene is located on chromosome 2 (2q14.1) and consists of 19 exons that encode a 999 amino acid protein with a predicted molecular weight of 110 kDa. The actual molecular weight is frequently larger due to N-linked glycosylation.

The MERTK receptor has an extracellular region, with two immunoglobulin-like-C2 (IgG-C2) and two fibronectin type III (FN-III) domains, and an intracellular region that includes a highly conserved tyrosine kinase domain (Fig. 1B). The extracellular region is similar in overall structure to adhesion molecules and binds the vitamin K-dependent modified ligands Gas6 and Protein S (ProS). X-ray crystallographic studies have shown that the IgG-C2 domains mediate binding of Gas6 to the TAM family members Axl and Tyro3. Gas6 also binds to Mertk, although with a lower affinity, presumably by docking with the IgG-C2 domains of the receptor. Both Gas6 and ProS appear to be expressed in the mouse outer retina and recent data indicate that mouse ProS can also activate mouse Mertk. Other results indicate that human ProS does not activate mouse Mertk. Species-specific differences in Mertk binding profiles or a requirement for ProS to bind to heterodimers of TAM receptors are possible explanations for this discrepancy.

2. Function

Mertk-deficient RCS rats and knockout mice have a severe progressive retinal dystrophy caused by a defect in RPE phagocytosis of outer segment (OS) tips. Mertk-deficient mice also exhibit abnormal clearance of apoptotic cells, one consequence of which is a marked persistence of apoptotic photoreceptor nuclei. Cell culture studies demonstrate that Mertk-deficient primary RPE cells have normal levels of OS binding, but are defective in the ingestion phase of phagocytosis. Accumulating evidence indicates that the underlying function of Mertk in OS ingestion by the RPE and clearance of apoptotic cells by macrophages is regulation of the cytoskeleton. When macrophages ingest Gas6-opsonized apoptotic cells, Mertk regulates cytoskeletal rearrangement through activation of the PLCγ and FAK, which in turn activates the p130Cas:Crk:Dock:Elmo complex and Rac (Tibrewal *et al.*, 2008). In the outer retina, the N-terminal portion of Gas6/ProS may bind to

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phosphatidylserine exposed on the outer membrane leaflet of shed OS, followed by binding of Gas6/ProS laminin G domains to Mertk and initiation of a signaling cascade leading to OS ingestion. Pharmacologic inhibition of PI3K in RPE cells results in diminished OS ingestion, suggesting that Mertk can also modulate the cytoskeleton via activation of the PI3K/Akt pathway. Recent studies from our laboratory demonstrate that Mertk drives redistribution of myosin II from the perijunctional F-actin belt to sites of OS binding, where myosin II function is required for normal OS ingestion (Strick *et al.*, 2009). Myosin II positioned at sites of OS ingestion could act in a manner similar to its role in FcγR-mediated phagocytosis by promoting the movement of pseudopodia used to enclose the phagocytic cargo. The mechanism by which Mertk mobilizes myosin II to sites of OS engulfment is unknown, but may involve activation of Rho GTPases, as is the case for recruitment of myosin II to the cleavage furrow during cytokinesis. Taken together, these data place Mertk at the center of cytoskeletal rearrangements necessary for phagocytic engulfment in disparate cell types.

The requirement for activation of Mertk via Gas6/ProS in both apoptotic cell uptake by immune cells and ingestion of shed OS by RPE cells in culture invites comparison of these two processes. The binding phases of both processes involve action of the αv class of integrin receptors and both processes are examples of ingestion of ‘self’ material. TAM receptor activation in antigen presenting cells has recently been shown to lead to inhibition of the innate immune response through blunting of both toll-like receptor signaling and cytokine production secondary to IFNα receptor activation. These and other findings provide an explanation for the progressive lupus-like autoimmune disorder seen in TAM receptor-deficient mice.

3. Disease Involvement

MERTK mutations are an infrequent cause of retinal dystrophy, accounting for about 1% of non-syndromic autosomal recessive cases. Of nine different mutant alleles identified in affected individuals, five were found to be homozygous due to consanguinity or, in one instance, uniparental isodisomy. The phenotype most commonly associated with *MERTK* mutations is severe rod-cone dystrophy, with the age at onset of symptoms described as ranging from 3 to 12 years (Mackay *et al.*, 2010). Disease progression is usually rapid, but function was relatively preserved in multiple individuals of one particular family at the end of the second decade, suggesting genetic or environmental modification. Night blindness, early macular involvement, and relative preservation of peripheral vision are commonly observed. Bull's eye macular lesions were seen in three families with different mutations. These findings, along with a distinctive appearance by spectral domain ocular coherence tomography, may allow increased ascertainment of individuals with retinal disease due to mutation of *MERTK*. Unlike in mice, there have been no reports of autoimmune symptoms in individuals with *MERTK* mutations.

Only one *MERTK* missense mutation (R844C) with a putative causative role in retinal disease has thus far been identified (McHenry *et al.*, 2004). Expression of MERTK 884C in cell culture demonstrated that the mutation reduced protein stability, resulting in diminished phosphorylation of putative downstream target proteins. These results, together with the fact that the other known *MERTK* mutations cause frameshifts, premature terminations, or splice site mutations leading to exon skipping, suggest that the underlying disease mechanism is loss of function of MERTK signaling.

4. Future Studies

The similarities between phagocytosis of apoptotic cells and OS tips raise the question: does Mertk help to down-regulate inflammatory responses in the RPE, as it does in immune cells?

This question is particularly intriguing because of the current interest in the role of RPE-localized inflammatory processes in the pathogenesis of age-related macular degeneration. Events upstream and downstream of Mertk activation during RPE phagocytosis also remain to be clarified. A role for Mertk ligands in OS phagocytosis in RPE cell and organ culture has been demonstrated, but a requirement for these proteins *in vivo* is lacking. The intermediate steps between Mertk activation and movement of myosin II to sites of OS ingestion, including possible actin cytoskeletal changes, are unknown. Another opportunity lies in gene replacement therapy for *MERTK*-associated retinal disease. Viral delivery of wild-type rat *Mertk* to the RPE of RCS rats *in vivo* can complement the phagocytic defect and slow photoreceptor degeneration, providing important preclinical evidence supporting a human trial. However, long-term efficacy of *MERTK* gene transfer has yet to be demonstrated in animal models.

Since the discovery a decade ago of its causal role in the retinal dystrophy of RCS rats, study of MERTK has illuminated the mechanism of mammalian phagocytosis and expanded our understanding of the causes of retinal degeneration in humans. It is likely that continued investigation of this interesting molecule will lead to further advances in both basic and applied knowledge in the future.

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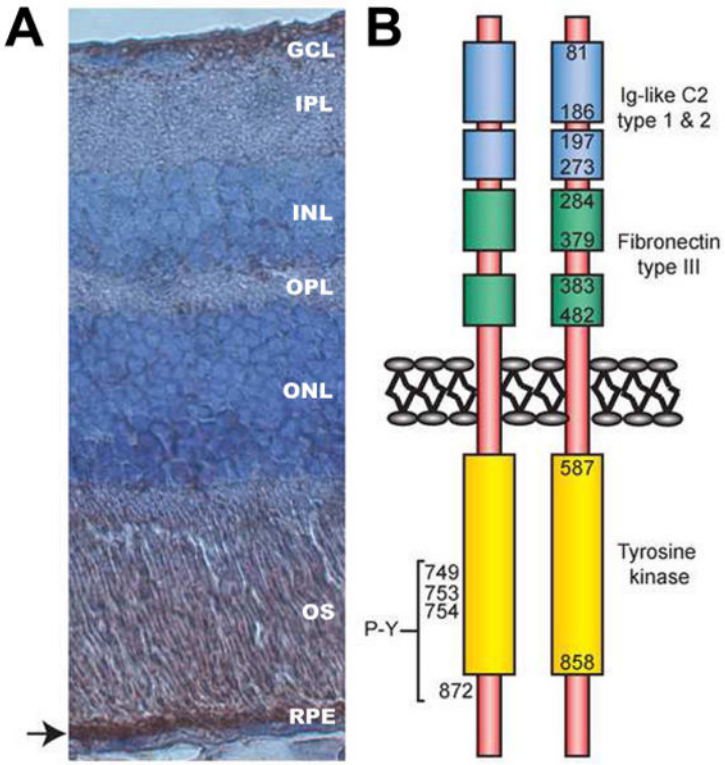

Figure 1.

A. Immunohistochemistry of a paraffin-embedded C57BL/6J mouse retinal section bleached with H_2O_2/formamide and stained with hematoxylin and an antibody directed against Mertk. Prominent staining is evident in the apical area of the RPE (arrow), above the RPE nuclei. GCL, ganglion cell layer; IPL, inner plexiform layer; INL, inner nuclear layer; OPL, outer plexiform layer; ONL, outer nuclear layer; OS, outer segment; RPE, retinal pigment epithelium. **B.** Protein domain structure of human MERTK. Numbers within the colored boxes indicate the extent of each domain (UniProt Database). Positions of key phosphotyrosine residues involved in MERTK signaling are indicated to the left.