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IMMUNE SIGNALLING

Waste sorting

Cells undergo apoptosis in both resting and inflamed tissues and must be rapidly cleared by phagocytes of the immune system; defects in this process can lead to tissue damage and autoimmunity. Zagórska *et al.* now show that the immune environment governs how an apoptotic cell is removed, with the TAM receptor protein kinases AXL and MER regulating apoptotic cell clearance in inflammatory and tolerogenic settings, respectively.

> “the immune environment governs how an apoptotic cell is removed”

The TAM family of receptors (TYRO3, AXL and MER) are expressed by phagocytes and promote the uptake of apoptotic cells by recognizing growth arrest-specific protein 6 (GAS6) and protein S, which bind to phosphatidylserine exposed on the surface of apoptotic cells. The authors found that treatment of bone marrow-derived macrophages (BMDMs) with dexamethasone, an immunosuppressive glucocorticoid, led to increased MER expression but decreased expression of AXL. By contrast, treatment of BMDMs with Toll-like receptor (TLR) ligands or pro-inflammatory cytokines led to a marked upregulation of AXL expression and a modest downregulation of MER expression. BMDMs stimulated with interleukin-4 also upregulated AXL, suggesting that the expression of this receptor is associated with diverse types of inflammation.

In keeping with this, untreated or dexamethasone-treated BMDMs required expression of MER, but not AXL, to phagocytose apoptotic cells. Conversely, uptake of apoptotic cells by BMDMs stimulated with the TLR3 ligand poly(I:C) was dependent on AXL, but not MER. Phagocytosis of apoptotic cells in these assays also required the presence of TAM receptor ligands, but although both GAS6 and protein S promoted MER-dependent phagocytosis, AXL-dependent phagocytosis was only stimulated by GAS6. Indeed, AXL itself was found to be crucial for maintaining tissue levels of GAS6, with a series of experiments indicating that GAS6 is normally found pre-bound to AXL.

Finally, the authors showed that activating antibodies specific for MER or AXL do not promote the phagocytosis of apoptotic cells in the absence of TAM ligands. In fact, these antibodies actually inhibited GAS6-stimulated phagocytosis, possibly by competing for receptor binding. However, the intravenous injection of AXL-specific activating antibodies inhibited type I interferon expression in lipopolysaccharide-treated mice, suggesting that these antibodies can mimic the anti-inflammatory effects of AXL signalling and could have therapeutic applications. Indeed, TAM inhibitors and activators are currently in development for clinical use and the authors' findings suggest that targeting AXL (which governs phagocytosis in inflammatory settings) may have fewer clinical side effects than targeting MER (which predominates in the steady state).

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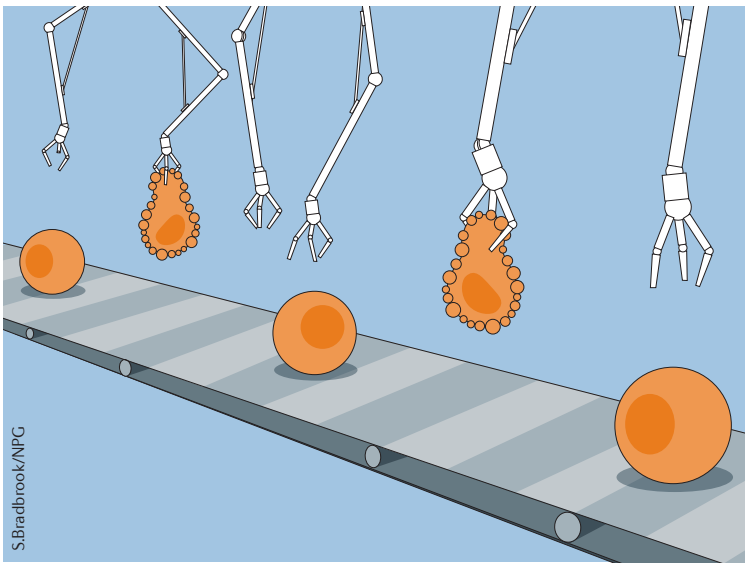

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ORIGINAL RESEARCH PAPER Zagórska, A. *et al.* Diversification of TAM receptor tyrosine kinase function. *Nature Immunol.* http://dx.doi.org/10.1038/ni.2986 (2014)