So, ligation of CD46 at a distal site alters normal DC-induced T-cell polarization and function.

These effects of CD46 ligation on polarization are not specific to T cells as they were also observed in natural killer (NK) cells. Ligation of CD46 prevented recruitment of the MTOC and perforin to the interface between the NK cell and its target cell and significantly reduced NK-cell cytotoxicity.

So, the data indicate that a competing external signal through CD46 can alter T-cell or NK-cell polarization towards DCs or target cells, which can inhibit lymphocyte function. An important question for further study is how many other signals can trigger competing axes of polarity. The authors suggest that this model might be a general mechanism by which lymphocytes determine which extracellular signals to respond to.

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AUTOIMMUNITY

Osteopontin: role in MS relapses

Between periods of disease remission, individuals with multiple sclerosis suffer distressing bouts of relapse and worsening of disease, eventually leading to a debilitating state. What determines the relapsing–remitting phases that characterize this devastating disease is a key unanswered question. Lawrence Steinman and colleagues now suggest that osteopontin could be a major player in triggering disease relapse, through its ability to promote the survival of autoreactive T cells.

Osteopontin is a pleiotropic cytokine that participates in a wide range of biological processes, such as bone remodelling, cancer and inflammation. Increased expression of osteopontin has been detected at sites of pathology in several autoimmune diseases, including in the brain lesions of patients with multiple sclerosis during disease relapse. This, together with the observation that mice deficient in osteopontin develop a milder form of experimental autoimmune encephalomyelitis (EAE; an animal model of multiple sclerosis) with fewer relapses, prompted the authors to assess whether osteopontin contributes to disease progression.

Using three models of multiple sclerosis, they showed that administration of recombinant osteopontin could indeed exacerbate disease. In osteopontin-deficient mice, a daily injection of osteopontin after the first phase of spontaneous remission of EAE triggered immediate relapse and led to severe fatal disease. Administration of osteopontin also worsened disease in wild-type mice with a relapsing–remitting model of EAE.

Because autoreactive T cells that infiltrate the central nervous system (CNS) are thought to be responsible for the pathology of EAE and because death of these cells has been associated with spontaneous remission, the authors assayed for T-cell death in CNS tissue sections from osteopontin-deficient and wild-type mice. They showed that osteopontin-deficient mice had more apoptotic cells in the CNS lesions than wild-type mice, indicating that osteopontin might support the survival of pathogenic T cells. To assess this further, they studied the effects of osteopontin on T cells *in vitro*. Osteopontin reduced cell death in cultures of wild-type activated T cells, and this was shown to be due to increased T-cell survival, as opposed to increased cell division.

So, how does osteopontin increase the survival of activated T cells? Treatment of T cells with osteopontin promoted activation of the pro-survival transcription factor NF-κB (nuclear factor-κB) while inhibiting activation of the pro-apoptotic transcription factor FOXO3A (forkhead box O3A). This effect was shown to be mediated by osteopontin-mediated phosphorylation of IκB kinase-β (IKKβ), which in turn phosphorylates both IκBα (inhibitor of NF-κB), leading to its degradation, and FOXO3A. Inhibition of the transcriptional activity of FOXO3A prevented expression of the pro-apoptotic factor BIM (BCL-2-interacting mediator of cell death), which is involved in activating the pro-apoptotic proteins BAK (BCL-2 antagonist/killer) and BAX (BCL-2-associated X protein). Finally, the anti-apoptotic effect of osteopontin was further illustrated by its ability to inhibit nuclear translocation of the mitochondrial protein AIF (apoptosis-inducing factor) — a feature of apoptotic cell death.

On the basis of these observations, the authors propose a model whereby the presence of osteopontin in the brain promotes disease progression, by protecting activated autoimmune T cells from cell death, which would otherwise provide an 'extra layer' of protection from severe autoimmunity. This role for osteopontin supports the idea that therapeutic targeting of this factor could restrain the progression of multiple sclerosis.

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ORIGINAL RESEARCH PAPER Hur, E. M. *et al.* Osteopontin-induced relapse and progression of autoimmune brain disease through enhanced survival of activated T cells. *Nature Immunol.* 3 December 2006 (doi:10.1038/ni1415).