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Review

GM-CSF in Neuroinflammation: Licensing Myeloid Cells for Tissue Damage

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Multiple sclerosis (MS) is the prototypical inflammatory disease of the central nervous system (CNS). MS lesions harbor different immune cells, but the contribution of individual cell types to disease etiology and progression is not well understood. In experimental autoimmune encephalomyelitis (EAE), auto-reactive helper T (Th) cells instigate CNS inflammation by acting on myeloid cells via the production of granulocyte-macrophage colony-stimulating factor (GM-CSF). Recent reports have implicated myeloid cells in both the inflammatory process and as executers of tissue damage in the CNS. We review these findings here, and integrate them into a model wherein GM-CSF produced by Th cells coordinates monocyte recruitment to the CNS, and differentiation into pathogenic effectors. We discuss the implications of this model to current therapies for MS, and outline important areas of further inquiry.

Which Cell Type Mediates Tissue Damage in Neuroinflammation?

Reports of the occurrence of so called 'neuroparalytic accidents' date back to the first rabies vaccine by Louis Pasteur. Vaccinated individuals often developed acute disseminated encephalomyelitis (ADEM), a disease resembling many features of multiple sclerosis (MS). The vaccine contained spinal cord extracts from rabbits and Thomas Rivers later discovered – in experiments involving primates – that the observed neuroinflammation was initiated by myelin components in the vaccine [1]. Thus, ADEM was driven by an autoimmune response against a myelin antigen (Ag). Experimental autoimmune encephalomyelitis (EAE) is the prototypical animal model for ADEM and MS, initiated by immunization with a myelin Ag. In 1981, Ben Nun and colleagues showed that transferring $CD4^+$ T cells from afflicted animals initiates EAE in healthy recipient animals (usually mice and rats), supporting the notion that MS is driven by myelin-reactive $CD4^+$ T cells [2]. Taken together with evidence that (i) particular type II major histocompatibility complex (MHC-II) alleles are associated with the highest risk for development of MS [3], (ii) minor risk alleles map to genes encoding proteins involved in T cell regulation [4], and (iii) blocking of T cell function is an effective therapy for MS, it is currently widely accepted that $CD4^+$ helper T (Th) cells are the prime mediators of MS in humans.

Let us consider the sequence of events following the adoptive transfer of pathogenic Th (ThPath) cells into a healthy mouse or rat. A scenario emerges wherein a myelin-reactive ThPath cell

Trends

Th cells can be categorized not only by the hallmark cytokines they express but also by the cell types they communicate with.

GM-CSF expression by autoreactive Th cells is crucial for their pathogenic potential and the activation of inflammatory phagocytes.

Multiple myeloid cells and their precursors sense GM-CSF during development and subsequent immune responses.

GM-CSF initiates inflammatory gene expression in monocytes and their progeny during an autoimmune episode.

Differentiated, inflammatory monocytes are highly abundant in inflamed tissue and represent major executers of GM-CSF-dependent pathogenesis.

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recognizes cognate Ag presented by a central nervous system (CNS) vessel-proximal antigen presenting cell (APC), but what happens next? How does target recognition of ThPath cells in the CNS lead to tissue destruction? Are the ThPath cells themselves capable of transecting axons or killing myelin-producing oligodendroglia? Or do ThPath cells recruit cytolytic $CD8^+$ T cells to carry out these functions? There is evidence both for Th cell mediated killing [5], and for $CD8^+$ cytotoxic lymphocyte invasion of the CNS parenchyma in MS and EAE [6]. Identifying the cellular effectors of CNS pathology and the mechanisms that trigger their activation could provide inroads into the treatment of MS and other conditions associated with inflammation and autoimmunity in the CNS. We examine the evidence supporting roles for different immune cell types in the pathogenesis of MS. When considering recent findings addressed in this article, we propose a model in which ThPath cells and their cytokines instruct myeloid cells to invade the CNS, where they constitute the effector cells that cause demyelination.

Effector Th Cells Communicate With Tissues or Myeloid Cells

Effector Th cells exist in different polarization states and have been categorized by their cytokine production profile and expression of transcription factors [7]. Several APC-derived polarizing factors have been implicated in the development of neuroinflammation, including interleukin (IL)-12, IL-23, IL-6, and IL-1 [8,9]. The biology of Th1, Th2, or Th17 and Th22 cells has been reviewed elsewhere with a focus primarily on their secreted cytokines [7,9]. However, rather than focusing on cytokine or gene expression signatures, Th cells can also be classified based on the cell types with which they communicate. Despite the apparent flexibility within supposedly stable lineages [10,11], the cytokines broadly expressed by different Th cells have identifiable patterns that transcend the name alone and define these cells functionally. For example, a RORγt (RAR-related orphan receptor γt)-dependent Th17 cell will express IL-17A, IL-17F, and also IL-22. IL-17 and IL-22 have been extensively shown to modulate lung, skin, and gut function both during inflammation and during tissue repair under homeostatic conditions [12,13]. When all available information is considered, these cytokines serve the immune system primarily by activating stromal cells and inducing an array of target genes, which in turn produce effector molecules that attract myeloid cells to inflammatory foci.

The situation is different for an interferon (IFN)-γ/GM-CSF-producing Th cell. Receptors for both IFNγ and GM-CSF (IFNGR and GM-CSFR) are abundant on neutrophils, dendritic cells (DCs), macrophages, and monocytes, and stimulation of myeloid cells by these cytokines induces the expression of an array of genes involved in cell differentiation and function, including numerous chemokines and inflammasome components [14,15]. Alternatively, GATA3 (GATA binding protein 3)-dependent Th2 cells mainly produce IL-4, IL-5, and IL-13, which impact on eosinophils and mast cells [16]. For the purposes of the present discussion, we propose grouping activated T cells according to the cellular targets of their communicative signals, rather than the cytokines they produce. Th17 cells communicate with $IL\text{-}17R^+IL\text{-}22R^+$ stromal cells to provide conditions for inflammatory cells to enter, whereas myeloid cells receive signals from distinct T cell subsets with their own differentiation requirements. Monocytes, macrophages, and DCs respond to T cells producing GM-CSF and IFNγ (ThPath cells), whereas IL-4, IL-5, and IL-13 act on eosinophils and mast cells (Figure 1).

Control of GM-CSF Expression in ThPath Cells

After it was shown that GM-CSF-deficient mice are resistant to EAE induction by myelin oligodendrocyte glycoprotein (MOG) immunization [17], more recent data connected T cell derived GM-CSF to disease progression and pathogenicity [18,19]. Adoptive transfer using cytokine-deficient mice showed that wild-type, $IL\text{-}17A^{-/-}$, and $IFN\gamma^{-/-}$ T cells induced EAE with similar kinetics. By contrast, $GM\text{-}CSF^{-/-}$ T cells were incapable of inducing EAE and invading the CNS [18]. In line with these findings, mice receiving $CD4^+GM\text{-}CSF^+$ T cells (sorted based on