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THE NEUROIMMUNOLOGY OF DEGENERATION AND REGENERATION IN THE PERIPHERAL NERVOUS SYSTEM

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Abstract—Peripheral nerves regenerate following injury due to the effective activation of the intrinsic growth capacity of the neurons and the formation of a permissive pathway for outgrowth due to Wallerian degeneration (WD). WD and subsequent regeneration are significantly influenced by various immune cells and the cytokines they secrete. Although macrophages have long been known to play a vital role in the degenerative process, recent work has pointed to their importance in influencing the regenerative capacity of peripheral neurons. In this review, we focus on the various immune cells, cytokines, and chemokines that make regeneration possible in the peripheral nervous system, with specific attention placed on the role macrophages play in this process.

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Key words: axotomy, chemokine, conditioning lesion, cytokine, dorsal root ganglion, macrophage.

INTRODUCTION

When an axon in the peripheral nervous system (PNS) is injured, a complex multi-cellular response occurs. The distal axonal segment degenerates, the cell body begins to express regeneration-associated genes (RAGs), and after a delay, the proximal segment forms a growth cone and begins to extend itself toward its denervated target. These processes of axonal degeneration and regeneration require changes not only in the injured neurons but also in non-neuronal cells including Schwann cells and immune cells. In this review, we have summarized recent advances in understanding these changes, focusing in particular on the role of chemokines, cytokines, and immune cells. One picture that will emerge is of macrophages playing two important roles in degeneration and regeneration by creating a pathway in the distal nerve segment conducive to axonal regeneration and by stimulating the axotomized neuronal cell bodies to switch to a regenerative phenotype (Fig. 1).

THE BIOLOGY OF WALLERIAN DEGENERATION (WD)

In 1850, Augustus Waller described changes he observed in axons of cranial nerves after they are disconnected from their cell bodies (Waller, 1850; reprinted in Stoll et al., 2002). The phenomena he described have been collectively termed WD and include among other phenomena the rapid disintegration of the distal axons and the subsequent influx of immune cells that rid the area of debris resulting from this breakdown. This process is thought to be necessary for successful regeneration to occur in the PNS (e.g., Gaudet et al., 2011). In the central nervous system (CNS), regeneration is inhibited perhaps in part because WD occurs much more slowly and myelin, which can inhibit regeneration, persists for years after axonal injury (for review see Vargas and Barres, 2007). The first sections of this review will focus on WD in the distal peripheral nerve segment in an effort to elucidate the role of macrophages in this process and the preparation for successful regeneration. The second half of the review will focus on changes in or surrounding the axotomized neuronal cell bodies and their impact on the conditioning lesion (CL) effect, a model of PNS regeneration. The studies cited throughout this review utilize

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Abbreviations: BDNF, brain-derived neurotrophic factor; BNB, blood–nerve barrier; CCL2, chemokine C–C motif ligand 2; CCR2, chemokine C–C motif receptor 2; CGRP, calcitonin gene-related peptide; CL, conditioning lesion; CNS, central nervous system; CNTF, ciliary neurotrophic factor; CR3, Complement receptor 3; CSPGs, chondroitin sulfate proteoglycans; DLK, dual leucine zipper kinase; DRG, dorsal root ganglion; DAMP, danger-associated molecular patterns; GAL3, galectin 3; GM-CSF, granulocyte–macrophage colony-stimulating factor; IFN-γ, interferon-γ; IL-1α, interleukin-1α; IL-1β, interleukin-1β; JAK, Janus kinase; JIP3, JNK-interacting protein 3; JNK, JUN amino-terminal kinase; LPC, lysophosphatidylcholine; MAG, myelin-associated glycoprotein; MCP-1, monocyte chemoattractant protein-1; MMP-9, matrix metalloproteinase-9; MIP-1α, macrophage inflammatory protein-1α; NAD+, nicotinamide adenine dinucleotide; NF-κB, nuclear factor kappa B; NGF, nerve growth factor; NLS, nuclear localization signal; Nmnat1, nicotinamide mononucleotide adenylyl transferase 1; PACAP, pituitary adenylate cyclase activating polypeptide; PLA2, phospholipase A2; PNS, peripheral nervous system; PSD, post-synaptic density; PTEN, phosphatase and tensin homolog; RAGs, regeneration-associated genes; RGCs, retinal ganglion cells; SARM-1, sterile alpha- and armadillo-motif-containing protein-1; SCG, superior cervical ganglion; SIRPα, signal regulatory protein α; SPRR1A, small proline-rich repeat protein 1A; STAT, signal transducer and activator of transcription; TNF-α, tumor necrosis factor α; TLR, toll-like receptor; Ube4b, E4 ubiquitin ligase; UPS, ubiquitin proteasome system; Wld^{s}, slow WD mouse; WT, wild-type; VIP, vasoactive intestinal peptide; WD, Wallerian degeneration.

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rodent sciatic nerve and/or dorsal root ganglion (DRG) unless otherwise stated.

Successful WD relies on a number of cell types (for reviews see Gaudet et al., 2011; Rotshenker, 2011). Almost immediately after peripheral nerve injury, Schwann cells dissociate from axons, dedifferentiate, and, along with fibroblasts, secrete cytokines that promote infiltration of immune cells. Neutrophils, the first immune cells to infiltrate, accumulate in the distal stump within 8 h, but their presence is short-lived (Perkins and Tracey, 2000). Subsequently, circulating monocytes are attracted to the injured nerve where they differentiate into macrophages, and within days these hematogenous macrophages take over as the dominant leukocyte population and have been thought to play a critical role in ensuring complete WD. Whereas many molecular and cellular mechanisms are involved in the coordination of WD, the very first changes are in the axon itself.

Within minutes after damage to the axonal membrane, Ca^{2+}-mediated proteolytic activity by the enzyme calpain initiates the breakdown of axons (George et al., 1995; for reviews see Coleman and Perry, 2002; Wang et al., 2012). Zhai et al. (2003) found that removal of extracellular Ca^{2+} delayed axonal degeneration in explanted superior cervical ganglion (SCG) for 16 h or longer and observed the earliest change in axons undergoing WD to be the fragmentation of microtubules. They also found that inhibition of the ubiquitin proteasome system (UPS) delays microtubule fragmentation both *in vivo* and *in vitro*. Recently, sterile alpha- and armadillo-motif-containing protein-1 (SARM-1), a member of the toll-like receptor (TLR) adaptor family, has been identified as important for injury-induced axon degeneration since a SARM knockdown was shown to protect axons in culture (Gerdts et al., 2013). SARM-1 may respond directly to an increase in axonal Ca^{2+} after axotomy as it is localized in the axonal compartment (Osterloh et al., 2012).

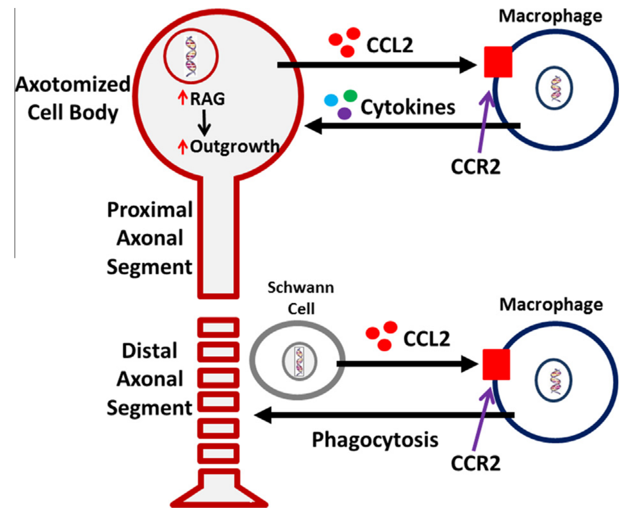

Fig. 1. A novel perspective on the response of macrophages to peripheral axotomy and their involvement in the regenerative response. Monocyte entry into a nerve, distal to the site of injury, is mediated through upregulation and release of the major monocyte chemokine, CCL2, by Schwann cells. Once the monocytes enter, beginning around 48 h post-injury, they differentiate into macrophages and phagocytose axonal and myelin debris resulting from the ongoing degenerative process. Removal of the debris, which is inhibitory to regenerating axons, is a known prerequisite for successful regeneration *in vivo*. Monocytes also enter into peripheral ganglia following nerve injury. Recent work has now suggested that macrophage presence around axotomized cell bodies helps mediate the conditioning lesion response. CCL2 is hypothesized to be the primary chemokine responsible for monocyte entry into the dorsal root ganglion. Under conditions in which macrophages do not enter the dorsal root ganglia, there is no enhanced growth after a conditioning lesion. Thus, there are two sites of action for macrophages in response to a peripheral nerve injury, in the distal nerve and around injured neuronal cell bodies.

Changes in cytokine and chemokine secretion in peripheral nerves after axotomy

Although axon degeneration is generally complete by 48 h after injury, this is only the beginning of WD. Certain products of early axonal degeneration, referred to as danger-associated molecular patterns (DAMPs), stimulate Schwann cells through TLRs leading to the breakdown of myelin and recruitment of macrophages (Vargas and Barres, 2007; Martini et al., 2008; Pineau and Lacroix, 2009). In addition to myelin breakdown in WD, there is an inhibition in new myelin synthesis. Within 24 h after nerve transection, there are decreases in the levels of mRNA for two myelin proteins, P_o and myelin basic protein, and by 5 d these mRNAs are no longer detectable (Trapp et al., 1988).

JUN, an immediate early gene, is rapidly upregulated in both neuronal cell bodies (Guertin et al., 2005) and Schwann cells, and its expression is increased by elevated intracellular Ca^{2+} levels (De Felipe and Hunt, 1994). This upregulation of *JUN* triggers a change in Schwann cell phenotype from myelinating to non-myelinating/immature, a process known as Schwann cell dedifferentiation (reviewed by Jessen and Mirsky, 2008). Lee et al. (2009) found that proteasome inhibition prevented Schwann cells from expressing dedifferentiation markers such as glial fibrillary acidic protein (GFAP) *in vitro* and *in vivo*. Axonal injury also initiates rapid activation (within 10 min) of the receptor tyrosine kinase erbB2 (Guertin et al., 2005), and increased expression of Notch intracellular domain within Schwann cells that enwrap the injured nerves, both of which promote dedifferentiation of Schwann cells and demyelination (Jessen and Mirsky, 2008). This dedifferentiation is critical as it allows Schwann cells to clear myelin and express cytokines important for successful WD. Interestingly, Napoli et al. (2012) found that expression of an inducible Raf-kinase in myelinating Schwann cells by itself is sufficient to drive dedifferentiation and cause demyelination, breakdown of the blood–nerve barrier (BNB), and influx of immune cells in the absence of injury signals derived from axon degeneration. These striking findings point to the importance of the mitogen-activated protein kinase (MAPK) cascade in Schwann cells in coordinating the molecular and cellular events in WD.

Due to their loss of contact with the axon, these dedifferentiated Schwann cells upregulate synthesis and secretion of tumor necrosis factor α (TNF-α) and interleukin-1α (IL-1α) within 5–6 h after injury (Shamash

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