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REVIEW

The role of primary infection of Schwann cells in the aetiology of infective inflammatory neuropathies

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Summary Numerous different pathogens are responsible for infective peripheral neuropathies and this is generally the result of the indirect effects of pathogen infection, namely anti pathogen antibodies cross reacting with epitopes on peripheral nerve, auto reactive T cells attacking myelin, circulating immune complexes and complement fixation. Primary infection of Schwann cells (SC) associated with peripheral nerve inflammation is rare requiring pathogens to cross the Blood Peripheral Nerve Barrier (BPNB) evade anti-pathogen innate immune pathways and invade the SC. Spirochetes *Borrelia bourgdorferi* and *Trepomema pallidum* are highly invasive, express surface lipo proteins, but despite this SC are rarely infected. However, *Trypanosoma cruzi* (Chaga's disease) and *Mycobacterium leprae*. Leprosy are two important causes of peripheral nerve infection and both demonstrate primary infection of SC. This is due to two novel strategies; *T. cruzi* express a trans-silalidase that mimics host neurotrophic factors and infects SC via tyrosine kinase receptors. *M. leprae* demonstrates multi receptor SC tropism and subsequent infection promotes nuclear reprogramming and dedifferentiation of host SC into progenitor stem like cells (pSLC) that are vulnerable to *M. leprae* infection. These two novel pathogen evasion strategies, involving stem cells and receptor mimicry, provide potential therapeutic targets relevant to the prevention of peripheral nerve inflammation by inhibiting primary SC infection.

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Introduction

Peripheral inflammatory neuropathy due to virus, bacterial, protozoa, parasites and spirochete infections are one of the most important global cause of potentially treatable neurological illness and disability.[1,2] The Schwann cell (SC) contributes an effective inflammatory anti pathogen response to combat infection by viruses and highly invasive spirochetes. By contrast, two obligate intracellular pathogens the protozoan *Trypanosoma cruzi* and *Mycobacterium leprae* are able to infect SC with persistent Peripheral nerve (PN) inflammation.[123] The pathogens and the invasive pathways underlying the vulnerability of SC are reviewed and are potentially important therapeutic targets; the pathogens and clinical examples of PN inflammation discussed in this review are given in Table 1.

The majority of systemic pathogens associated with peripheral nerve (PN) inflammation do not primarily infect SC or other cellular components of peripheral nerve. Therefore, PN inflammation due to systemic pathogens results from the indirect effects of pathogen infection of PN and include the formation of anti-pathogen antibodies forming immune complexes, these cross from the systemic circulation into the nerve resulting in demyelination and axonal injury.[3,4] Molecular mimicry is a proposed mechanism that triggers peripheral nerve inflammation after systemic infection and vaccination with several pathogens (*Campylobacter jejuni*, Epstein Bar and Cytomegalo viruses).[4–9] and relies upon the structural similarity between microbial antigens and host tissues. The T cells and complement fixing antibodies generated against the pathogen cross react with antigen located on the axon and SC producing macrophage and T cell infiltration into the nerve with an axonal motor and demyelinating neuropathy known as Guillian Barre syndrome (GBS).[5–9]

On this basis Peripheral nerve (PN) inflammation in the context of infection is generally considered to be the result of indirect (secondary) effects of the pathogen activating cellular constituents of PN (Schwann cells fibroblasts, macrophages).[10] Pivotal to this response is the SC because it provides an important component of the adaptive and innate immune response directed against invading pathogens.[10,11] Viral infection of SC has been described *in vitro* but clinical examples in non-immune suppressed cases are rare, this relates in part to the effective barrier between the SC and systemic circulation (the BNPB) and the range of pattern recognition receptors (PRR) capable of detecting virus and initiating an effective anti virus response.[11–13] Similarly, *Trepomema pallidum (Syphilis) Borrelia burgdorferi* (Lyme disease) are associated with peripheral neuropathies but the SC produces an effective anti spirochete response and this prevents intracellular infection.[13–15] Despite an anti pathogen inflammatory response by SC *T. cruzi* (Chaga's disease) is capable of invading the SC and stimulating chronic inflammation and injury to the Autonomic nervous system (ANS).[16–18] The same is true for PN Leprosy *M. leprae* with extensive intracellular SC infection and chronic destructive inflammation, despite a significant innate and adaptive immune response.[19–22]

Schwann cells are especially vulnerable to *M. leprae* infection and this pathogen also disseminates throughout the PNS and other tissues.[22] The conventional view that SC has a limited response to pathogen attack and restricted to an inflammatory response has been revised in view of recent *in vitro* evidence demonstrating a novel interaction between *M. leprae* and SC based upon pathogen initiated nuclear reprogramming.[23,24] This data has provided new insights into the contribution of the SC in the aetiology of peripheral nerve inflammation following infection and this takes into account the functional properties of SC especially the capacity for proliferation during PN repair following injury.[25]

Although the treatment of peripheral nerve inflammation due to pathogens relies upon antibiotics and anti inflammatory agents.[26] The identification of a novel pathogen—SC interaction[24] associated with peripheral nerve inflammation could provide new and important therapeutic targets.

Schwann cell structure and function; the blood peripheral nerve barrier (BPNB) endoneurium and immune privileged space

The perineurium a connective tissue layer surrounds the compartment (endoneurium) containing the SC and axons and this presents a physical barrier to systemic pathogen invasion (see Fig. 1).[19,27] It is composed of flat cells interconnected by tight junction complexes (TJ) containing the structural proteins claudins (1, 3, 3-3), occludins and Zo1.[28–31] Capillaries penetrate the perineurium and are distributed in the endoneurium; they are composed of non-fenestrated sheets of endothelial cells with an occasional pericyte contributing to the BPNB.[28] The individual endothelial cells are interconnected by tight junctions (TJ) to form a non-fenestrated and non-permeable barrier and this is analogous to the blood brain barrier (BBB) surrounding the CNS.[12,28]

The endoneurium contains SC, mast cells, macrophages and fibroblasts all capable of expressing a range of trophic factors[32] important for axonal regeneration and SC plasticity/proliferation, together with several signalling pathways to support axonal repair and remyelination.[33–35]

Schwann cell inherent plasticity is essential for myelination and provides a vulnerable cell population for infection

Schwann cells are derived from the embryonic neural crest day 19 *in utero* (Fig. 1). After birth the SC retain their inherent plasticity and differentiate into non-myelinating and myelinating populations controlled by signalling pathways between axon and SC.[25,27] Schwann cell differentiation into mature myelinating cells is pivotal for remyelination and this is under the control of several transcription factors including Sox 10 (found in early development and glial cell development).[25,33–35] Intra cellular SC pathogen infection will potentially disrupt these pathways preventing SC differentiating into cells capable of supporting re myelination and axon repair; this is an important factor in the relationship between SC and intracellular infection.