Chapter C8

CORONAVIRUS-INDUCED DEMYELINATION AND SPONTANEOUS REMYELINATION

Growth factor expression and function

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Abstract: MHV-A59 coronavirus infection produces a transient episode of demyelination that is followed by spontaneous remyelination. This paradigm provides a complex lesion environment to examine cellular and molecular mechanisms involved in successful CNS remyelination. Our work in this model has focused on the roles of platelet-derived growth factor and fibroblast growth factor 2 in regulating oligodendrocyte progenitor responses required for remyelination.

Key words: platelet-derived growth factor, fibroblast growth factor, estrous cycle, gender, demyelinating disease, remyelination, coronavirus, cuprizone

1. INTRODUCTION

Insufficient remyelination results in prolonged neurological impairment in demyelinating disease states, such as multiple sclerosis. A critical determinant of remyelination is regulation of oligodendrocyte lineage responses. Surviving and/or newly generated oligodendrocyte lineage cells must be recruited to appropriate sites within demyelinated tissues and induced to differentiate and form myelin. Each of these oligodendrocyte lineage cell responses appears to be regulated by signals within the lesion environment, such as growth factors, cytokines, and cell-cell interactions.

The pathology of multiple sclerosis (MS) lesions is heterogeneous between patients, with at least four fundamentally different patterns of
demyelination (12). Therefore, analysis of experimental models of
demyelination with distinct mechanisms of pathogenesis is warranted. In
addition, different experimental models have advantages for examining
specific aspects within the course of demyelinating diseases. The mouse
model of murine hepatitis strain A59 (MHV-A59) coronavirus infection
serves as a relevant model for analyzing the cellular and molecular
components involved in spontaneous remyelination. The complexity of
MHV-A59 lesions includes infiltration of CD8+ and CD4+ T cells, B
lymphocytes producing immunoglobulins, macrophages, and reactive glial
cells (15,21). These lesion components are variably exhibited among
categories of MS lesions.

The potential function of molecules that can promote remyelination in MS
lesions, such as growth factors, is ideally analyzed in the context of a
complex lesion environment due to contributing effects of cytokines,
chemokines, infiltrating lymphocytes, and reactive cells. However, this
complex lesion milieu can also make it difficult to delineate effects that are
specific to the remyelination process. For this purpose, analysis of
oligodendrocyte lineage responses is facilitated by comparison with a
simpler lesion model, such as ingestion of cuprizone (14). Growth factor
effects common to experimental lesions of diverse pathogenesis, such as
MHV-A59 and cuprizone models, are most likely to be applicable more
generally to demyelinating diseases.

This chapter will review recent findings of the expression and function of
specific growth factors in MHV-A59 and cuprizone models of spontaneous
remyelination. In addition, the complexity of the MHV-A59 model will be
exemplified by discussion of the modulation of the disease course in
correlation with gender and estrous cycle status. This modulation of the
MHV-A59 disease course is also relevant to modulation of MS disease
activity.

2. DISEASE SEVERITY IN THE MHV-A59 MODEL

Intracranial infection of female C57Bl/6 mice at 28 days of age with 1000
plaque forming units (PFU) of MHV-A59 virus produces a characteristic
progression of demyelinating disease. Demyelination begins within the first
week post-injection (wpi), with more extensive areas of myelin degeneration
by 2 wpi (1,9). During this progression of demyelination, mice exhibit loss
of motor function, and virus is present in cells of the white matter (9). In
subsequent weeks, clearance of virus and myelin debris occurs,
remyelination is initiated, and recovery of motor function proceeds (9,21).
However, among mice similarly infected with MHV-A59, there is variability
in the proportion of mice that exhibit distinct results from asymptomatic,