CHAPTER 8

Heat Shock Proteins in Multiple Sclerosis

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Abstract

In this review, we have addressed the possible contribution of heat shock proteins (HSP) to the pathogenesis of multiple sclerosis (MS), a chronic inflammatory demyelinating disease of the central nervous system (CNS). A particular focus of the review is on the families of HSP27, HSP60 and HSP70 because there is good evidence for both RNA and protein that expression levels of these HSP are altered in lesioned areas of the CNS. Using a variety of different approaches, the data support a role for these HSP in the generation of the immune response, particularly in the more chronic phases of the disease process. In addition, we review evidence supporting a protective role for these HSP in the injured CNS. This dual role of HSP makes an analysis of their effects in degenerative CNS diseases difficult to determine with certainty. Nevertheless, ongoing data are persuasive that this remains an important area of research that is likely to continue to contribute to our understanding of disease pathogenesis in MS.

Introduction

Multiple sclerosis is a degenerative condition of the central nervous system (CNS) that affects approximately 10^6 persons worldwide. Disease onset is usually first noted in young adulthood and epidemiological studies have shown that people in higher latitudes are more frequently affected. In the early stages, disease activity usually displays a relapsing-remitting course, but with time patients enter a secondary progressive phase with increasing evidence of disability. Clinical symptoms depend upon the location of pathological lesions within the CNS and can vary significantly. The clinical diagnosis of MS requires two features: dissemination of the disease in space and in time. The first criterion can be achieved by demonstration on MRI examination of disseminated lesions throughout the CNS, whereas the second criterion requires either occurrence of a second clinical episode or a new lesion on MRI image that presents after the onset of the initial symptoms. In the CNS, lesions are predominantly located in white matter tracts, particularly at periventricular sites. Acute active lesions are characterized by loss of myelin in the presence of a mononuclear inflammatory infiltrate centered around vessels consisting of activated lymphocytes and macrophages. Elevated levels of immunoglobulins and complement components have also been detected in the lesion as well as in cerebrospinal fluid (CSF). Older lesions show less evidence of ongoing inflammatory activity, and are characterized by demyelinated axons embedded in an astrocytic scar, reduced numbers of oligodendrocytes, and variable axonal loss.1-3

The presence of activated lymphocytes and immunoglobulins within the lesions and in the CSF have suggested that MS may have an immune component, and animal models have demonstrated that sensitization against CNS tissues leads to an inflammatory demyelinating
disease that displays many of the clinical and pathological characteristics of MS. Indeed, it is now well accepted that antigens associated with the myelin sheath or with the myelin forming cell the oligodendrocyte, such as myelin basic protein (MBP), proteolipid protein (PLP) and myelin oligodendrocyte glycoprotein (MOG) are potent antigens, eliciting both T and B cell responses that, to varying degrees, can either alone or in concert passively transfer disease activity to naïve animals. Using well-defined antigens, or specific peptides derived from these antigens, further studies in animals have indicated that CD4+ T cells displaying a Th1-like cytokine profile are critical for disease expression, whereas CD4+ T cells expressing Th2-type cytokines may be protective. Of particular note for the subject matter of this chapter is the observation that animals that display a relapsing-remitting course show a switch in the predominant myelin antigen to which they respond as the disease progresses, a phenomenon known as epitope spreading, and for which there is now compelling evidence that this reflects de novo sensitization to myelin and possibly nonmyelin antigens within the inflamed CNS.

These data have led to the concept that MS may represent an autoimmune disease mediated by T cells directed against myelin antigens, perhaps exacerbated by the presence of antibodies directed against the same or even different myelin-specific antigens. However, subsequent studies showed that myelin autoreactive T cells can be found in the circulation of most healthy individuals, raising the possibility that in MS it is a failure of normal immunoregulatory circuits that keep autoreactive T and B cells in check, which leads to disease expression.

Autoimmune responses could, therefore, account for the myelin and oligodendrocyte loss, but at the present time autoimmune responses have not been implicated in initiating the axonal loss. Rather, this is thought to reflect the severity of the inflammatory response and the formation or release of toxic factors, such as peroxynitrites and glutamate, within the lesion.

The question that arises in the context of this current volume is how might heat shock proteins (HSP) contribute to the pathogenesis of MS? The term HSP covers a number of different families of proteins that are generally classified according to their molecular weight. Although historically defined by their upregulation in response to heat or stress, the constitutive expression of some HSP during embryogenesis and in the adult suggest a role in normal development and differentiation. HSP participate in protein synthesis and in the organization, structural stability, and anchoring of the cytoskeleton in both stressed and unstressed cells. These associations, mediating correct assembly and stabilizing proteins at times of vulnerability to denaturation, while not becoming integral components of the mature assembled structures, has earned them the designation of molecular chaperones or chaperonins.

Certain HSP, particularly HSP60 and HSP70, have been found to elicit strong immunological reactions. In many bacterial and parasitic infections, these proteins are significantly upregulated following invasion of the host, and immune responses against them are common. The fact that these HSP of bacterial and parasitic origin share significant sequence homology with mammalian HSP has suggested that the expression of these proteins on stressed host cells may contribute to the development of autoimmunity. In this review, we will focus on the data that support a potential role for HSP in the immune and inflammatory responses that contribute to MS and/or its animal model experimental autoimmune encephalomyelitis (EAE). Most of these data have been collected for members of the 27 kD/α-B crystallin, 60 kD and 70 kD families, and this review will be focused on these HSP. This is not to say that other HSP such as gp96 are not involved in MS or its animal model EAE, but that at the present time there is less information that supports such an involvement.

The Small Heat Shock Proteins

In mammalian cells the small heat shock proteins represent a relatively small family of proteins with molecular weights of 20-28 kD in mice and 20-28 kD in humans. The αB crystallin of the lens has been shown to share significant sequence homology with HSP27 and is considered a member of this family. The small HSP are expressed constitutively in a predominantly nonphosphorylated form in many cell types and as a multimeric 200 to 800 kD