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Review

The protective role of prosaposin and its receptors in the nervous system

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ABSTRACT

Prosaposin (also known as SGP-1) is an intriguing multifunctional protein that plays roles both intracellularly, as a regulator of lysosomal enzyme function, and extracellularly, as a secreted factor with neuroprotective and glioprotective effects. Following secretion, prosaposin can undergo endocytosis via an interaction with the low-density lipoprotein-related receptor 1 (LRP1). The ability of secreted prosaposin to promote protective effects in the nervous system is known to involve activation of G proteins, and the orphan G protein-coupled receptors GPR37 and GPR37L1 have recently been shown to mediate signaling induced by both prosaposin and a fragment of prosaposin known as prosaptide. In this review, we describe recent advances in our understanding of prosaposin, its receptors and their importance in the nervous system.

Contents

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1. Introduction

A number of secreted factors, including a variety of proteins, peptides, bioactive lipids and other types of molecules, are capable of exerting protective actions on neurons and glia in the nervous system. Such protective factors and their receptors have garnered significant research interest for their potential as therapeutic targets in the treatment of neurological damage and disease (Allen et al., 2013; Schulte-Herbruggen et al., 2008). One of the largest and most intensively-studied families of protective factors is the neurotrophins, which includes nerve growth factor, brain-derived neurotrophic factor and several other secreted proteins that act predominantly through receptor tyrosine kinases (Chao, 2003). Other protective factors, including ciliary-derived neurotrophic factor (CNTF) and interleukin-6, signal through cytokine receptors coupled to the JAK/STAT pathway (Bauer et al., 2007). In addition to these distinct classes of neurotrophic factors, there are also a number of unique protective factors that demonstrate potential in the treatment of nervous system injuries and neurological disorders. One such unique factor, which has been studied for more than 20 years in terms of its protective actions on neurons and glia, is prosaposin.

2. The function of prosaposin and the saposins

2.1. *Prosaposin as a lysosomal protein*

Prosaposin was initially identified as the precursor protein for four lysosomal activator proteins known as the saposins A–D (Kishimoto et al., 1992). Saposins were named due to their actions as sphingolipid activator proteins that facilitate the hydrolysis of sphingolipids via lysosomal hydrolases (Kishimoto et al., 1992). Interest in the saposins began in the 1960s with the discovery of saposin B (Mehl and Jatzkewitz, 1964) followed by the discovery of saposin C in 1971 (Ho and O'Brien, 1971). Saposin B, also known as SAP-1, was isolated and cloned in the mid-1980s (Dewji et al., 1986; Isemura et al., 1984). Not long after, the prosaposin precursor protein was sequenced and identified as a homolog of the rat sulfated glycoprotein 1 (SGP-1) (Collard et al., 1988; O'Brien et al., 1988) and the mouse testicular sulfated glycoprotein 1 (Morales et al., 1998).

Each of the four saposins has a distinct role in promoting hydrolysis of sphingolipids, and this facilitation of hydrolysis is thought to be a result of saposin-induced remodeling of lysosomal membranes. Saposins A and C have been shown to enhance β-glucosylceramidase-mediated hydrolysis of glucocerebroside as well as hydrolysis of galactocerebroside (Morimoto et al., 1989; Wenger et al., 1982). Saposin A primarily acts by optimizing the hydrolysis of galactocerebrosides via β-galactosylceramidase (Harzer et al., 1997) whereas saposin C enhances β-glucosidase activity and protects the enzyme from proteolytic degradation (Qi and Grabowski, 1998; Sun et al., 2003). Saposin B enhances hydrolysis of galactocerebroside sulfate (Fischer and Jatzkewitz, 1975), GM1 ganglioside (Inui and Wenger, 1984), and globotriaosylceramide (Gartner et al., 1983; Li et al., 1985), and also promotes glycerolipid hydrolysis (Li et al., 1988). Finally, saposin D has been shown to enhance the hydrolysis of sphingomyelin by sphingomyelin phosphodiesterase (Morimoto et al., 1988). The precise molecular mechanisms by which the saposins promote the lysosomal processing of lipids are still a point of significant research interest, but direct saposin interactions with lipids appear to be important (Kishimoto et al., 1992; Soeda et al., 1993). Saposins may act as "solubilizers", which facilitate the extraction of substrate lipids from lysosomal membranes for presentation to hydrolase enzymes, and/or as "liftases", which enhance enzyme access to substrate lipids via saposin-induced membrane remodeling. Support for the "solubilizer" and "liftase" models comes from a number of studies demonstrating saposin binding to substrate lipids and membrane remodeling induced by saposins (Alattia et al., 2006; Vaccaro et al., 1993; Vogel et al., 1991) Similarly, saposin binding to lipids has been shown to be crucial for lipid loading of CD1, which is necessary for CD1-mediated antigen presentation and immune system recognition of lipid-based antigens on pathogens (Kang and Cresswell, 2004; Leon et al., 2012; Zhou et al., 2004).

Dysfunction or loss of saposins can result in an assortment of lysosomal storage diseases. Saposin A dysfunction has been linked to development of globoid cell leukodystrophy (GLD), also known as Krabbe disease (Matsuda et al., 2001; Spiegel et al., 2005), largely through reports that mice deficient in saposin A also exhibit a Krabbe disease phenotype(Matsuda et al., 2007) and exhibit nervous system deficits including neurological deficits, hindlimb weakness, and a demyelination phenotype (Matsuda et al., 2001). This was further confirmed by a clinical report of abnormal myelination in an infant diagnosed with Krabbe disease and deficient in saposin A (Spiegel et al., 2005). Furthermore, leukocytes from this patient demonstrated an abnormality of galactocerebrosidase activity, which was linked to a three base pair deletion in the saposin A coding region of prosaposin (Spiegel et al., 2005).

Mice deficient in saposin A as well as saposin B display motor deficits including tremor and foot slips and aberrant locomotor activity (Sun et al., 2013). Additionally, these mice