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Review

Diverse functional roles of lipocalin-2 in the central nervous system

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ABSTRACT

Lipocalin-2 (LCN2) is an acute phase protein with multiple functions that has garnered a great deal of interest over the last decade. However, its precise role in the pathophysiology of the central nervous system (CNS) remains to be outlined. Emerging evidence indicates that LCN2 is synthesized and secreted as an inducible factor from activated microglia, reactive astrocytes, neurons, and endothelial cells in response to inflammatory, infectious, or injurious insults. More recently, it has been recognized as a modulatory factor for diverse cellular phenotypes in the CNS, such as cell death, survival, morphology, migration, invasion, differentiation, and functional polarization. LCN2 induces chemokine production in the CNS in response to inflammatory challenges, and actively participates in the innate immune response, cellular influx of iron, and regulation of neuroinflammation and neurodegeneration. LCN2 also modulates several biobehavioral responses including pain hypersensitivity, cognitive functions, emotional behaviors, depression, neuronal excitability, and anxiety. This review covers recent advances in our knowledge regarding functional roles of LCN2 in the CNS, and discusses how LCN2 acts as an autocrine mediator of astrocytosis, a chemokine inducer, and a modulator of various cellular phenotypes in the CNS. We finally explore the possibilities and challenges of employing LCN2 as a signature of several CNS anomalies.

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1. Introduction

The lipocalins are a large family of proteins mainly composed of extracellular ligand-binding proteins with a high specificity for small hydrophobic molecules (Flower, 1994, 1996; Flower et al., 1993, 2000; Ganfornina et al., 2000; Pervaiz and Brew, 1985). The lipocalin protein family contains over 20 small, soluble, and mostly extracellular proteins, which transport small hydrophobic molecules like steroids, bilins, retinoids, and lipids. The protein family shares a region of sequence homology and a common tertiary architecture (Cowan et al., 1990; Dittrich et al., 2013; Flower, 1996; Flower et al., 1993; Godovac-Zimmermann, 1988; Pervaiz and Brew, 1987; Salier, 2000). Despite sequence diversity, many proteins in the lipocalin family have a similar three-dimensional structure, which is composed of a single eight-stranded and continuously hydrogen-bonded anti-parallel β-barrel (Flower et al., 2000). The β-barrel binds and transports lipophilic ligands, such as retinoids and fatty acids (Flower, 1996). In addition, lipocalins can bind to specific cell-surface receptors and may deliver ligands, including iron, growth or survival factors, to the cell by receptor-mediated endocytosis (Flower et al., 2000). Lipocalins play an important role in biological processes such as immune responses, control of cell migration, proliferation, and differentiation as well as olfaction, pheromone and retinol transport, retinoid binding, cryptic coloration, and enzymatic synthesis of prostaglandins (Flower, 1994). Lipocalins are also implicated in the regulation of cell homoeostasis and general clearance of endogenous and exogenous compounds (Flower, 1996).

Lipocalin-2 (LCN2), also known as neutrophil gelatinase-associated lipocalin (NGAL) (Rudd et al., 1999), 24p3 (Flower et al., 1991) or 24-kDa superinducible protein (SIP24) (Hamilton et al., 1985), is a member of the lipocalin family (Flower et al., 2000; Kjeldsen et al., 2000). A murine form of the protein (24p3) was identified with a 62% homology in amino acid sequence (Cowland and Borregaard, 1997). Previous studies have suggested that LCN2 protects neutrophil gelatinase from auto-degradation (Yan et al., 2001). LCN2 may also function as an acute-phase protein (Liu and Nilsen-Hamilton, 1995). Marques et al. (2008) suggest that LCN2 is produced by the choroid plexus as a component of the innate immune response and protects the central nervous system (CNS) from infection. LCN2 is expressed frequently in tissues prone to pathogen exposure. It is most prominently expressed in secondary granules of neutrophils (Axelsson et al., 1995; Borregaard et al., 2007). LCN2 binds to two cell-surface receptors: brain type organic cation transporter (24p3R) and megalin (Devireddy et al., 2005; Richardson, 2005; Schmidt-Ott et al., 2007). The 24p3R is expressed constitutively and is present at particularly high levels in kidney epithelial cells (Devireddy et al., 2005), epithelia of respiratory and alimentary tracts (Cowland and Borregaard, 1997; Friedl et al., 1999), macrophages, neutrophils (Eller et al., 2013; Jha et al., 2014a), microglia (Lee et al., 2007), astrocytes (Lee et al., 2009) and neurons (Jeon et al., 2013). Megalin, a multi-ligand endocytic receptor, is heavily expressed in a group of absorptive epithelial cells, including renal proximal tubule, epididymal and thyroid cells (Cabezas et al., 2011; Christensen and Birn, 2001, 2002; de Barros Peruchetti et al., 2014; Kerjaschki and Farquhar, 1982; Li and Zhuo, 2014; Marino et al., 2001; Marzolo and Farfan, 2011; Suzuki et al., 2013; Zheng et al., 1998), gallbladder (Erranz et al., 2004) and neuroepithelium (Spoelgen et al., 2005; Willnow et al., 1996). Megalin is also expressed in T lymphoid and erythroid cells as well as granulocyte/macrophage lineage cells (Miharada et al., 2008). Megalin expression in the CNS is restricted to the brain capillaries, choroid plexus (Carro et al., 2005; Chun et al., 1999), the ependymal cells of the lateral ventricles (Gajera et al., 2010), neural progenitors in embryonic mouse spinal cord (Wicher et al., 2005), neural tube floor plate cells (Kur et al., 2014; McCarthy et al., 2002), postnatal mouse spinal cord oligodendrocytes (Wicher et al., 2006), retinal ganglion cells (Fitzgerald et al., 2007) and cultured astrocytes (Bento-Abreu et al., 2008, 2009) as well as neurons (Ambjorn et al., 2008; Chung et al., 2008; Fleming et al., 2009). During the development of oligodendrocyte precursor cells, megalin is selectively expressed by optic nerve astrocytes (Ortega et al., 2012). Sensory organs like the inner ear (Konig et al., 2008; Mizuta et al., 1999) and eye (Assemat et al., 2005; Fisher and Howie, 2006; Lundgren et al., 1997) also express megalin.

Recent studies have shown an increased expression and an important role of LCN2 in various pathological states, including cancerous conditions like breast cancer (Leng et al., 2011; Wenners et al., 2012; Yang et al., 2009, 2013a), leukemias (Bouchet and Bauvois, 2014), pancreatic ductal adenocarcinoma (Leung et al., 2012), oral cancer (Lin et al., 2012; McLean et al., 2013), colorectal cancer (Marti et al., 2013; Reilly et al., 2013), as well as multifaceted cancer (Devarajan, 2007; Li and Chan, 2011; Rodvold et al., 2012; Yang and Moses, 2009); kidney diseases like acute kidney injury (Barrera-Chimal and Bobadilla, 2012; Haase et al., 2009; Verna et al., 2012), chronic kidney disease (Hashikata et al., 2014; Nickolas et al., 2008; Renders and Heemann, 2012), congenital obstructive nephropathy (Becknell et al., 2013), kidney ischemia reperfusion injury (Grigoryev et al., 2013; Kaminska et al., 2011), virus-associated nephropathy (Rau et al., 2013), lupus nephritis (Rubinstein et al., 2008; Schwartz et al., 2007); liver dysfunctions like acute liver injury (Borkham-Kamphorst et al., 2013; Melino et al., 2012; Mishra et al., 2005), acute hepatic failure (Roth et al., 2013), fatty liver disease (Auguet et al., 2013; Semba et al., 2013); cardiovascular diseases like chronic heart failure (Naude et al., 2014), autoimmune myocarditis (Ding et al., 2010), atherosclerosis (Iqbal et al., 2013; Wu et al., 2013; Xiao et al., 2013), coronary artery disease (Lee et al., 2010), endothelial dysfunction and hypertension (Song et al., 2014; Wang, 2012); diabetes (Jang et al., 2012; Xiao et al., 2013; Yan et al., 2007) and obesity (Song et al., 2014; Taube et al., 2012; Wang, 2012; Wu et al., 2013; Yan et al., 2007; Zhao and Stephens, 2013); psoriasis (an immune-mediated skin disease) (Ataseven et al., 2014), and diverse inflammatory conditions (Cockayne et al., 2012; Conde et al., 2011; Fritsche et al., 2012; Guglani et al., 2012; Li and Chan, 2011; Ostvik et al., 2013). Similarly, LCN2 is also expressed (and plays a pivotal role) in CNS

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