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Review

The CD24 surface antigen in neural development and disease

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ABSTRACT

A cell's surface molecular signature enables its reciprocal interactions with the associated microenvironments in development, tissue homeostasis and pathological processes. The CD24 surface antigen (heat-stable antigen, nectadrin; small cell lung cancer antigen cluster-4) represents a prime example of a neural surface molecule that has long been known, but whose diverse molecular functions in intercellular communication we have only begun to unravel. Here, we briefly summarize the molecular fundamentals of CD24 structure and provide a comprehensive review of CD24 expression and functional studies in mammalian neural developmental systems and disease models (rodent, human). Striving for an integrated view of the intracellular signaling processes involved, we discuss the most pertinent routes of CD24-mediated signaling pathways and functional networks in neurobiology (neural migration, neurite extension, neurogenesis) and pathology (tumorigenesis, multiple sclerosis).

Contents

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1. Introduction

The biological significance of the CD24 surface antigen is reflected by the diversity of processes in which it has been implicated, from regulating lymphocyte development (Allman et al., 1993), to altering cancer cell interactions (Aigner et al., 1998; Kristiansen et al., 2004; Lee et al., 2009), to modulating neurite outgrowth (Kleene et al., 2001; Shewan et al., 1996). Research in immunology, tumor biology and neuroscience has demonstrated the critical importance of CD24 for this broad, seemingly unrelated set of processes (Fang et al., 2010). Here, we examine the molecular structure and role of CD24 in neurobiology, including its spatiotemporal expression dynamics during neural development (Calaora et al., 1996; Shirasawa et al., 1993), its connection to signaling pathways, and its relevance for pathophysiological processes, most notably multiple sclerosis (Braliou et al., 2015; Huang et al., 2015) and neural malignancies (Deng et al., 2012; Kristiansen et al., 2004).

Conserved across many mammalian species (Ayre et al., 2016), CD24 was first identified in mice in 1978 and named the heat stable antigen for its resistance to heat-induced denaturation (Springer et al., 1978). Other names for the associated epitope include nectadrin and P31, with mCD24 occasionally used to refer to the mouse ortholog. The first functions attributed to CD24 were related to cell adhesion (Kadmon et al., 1992) and to immune cell differentiation, following the observation that CD24 is highly expressed in lymphocyte progenitors, but absent in activated B-cells and mature T-cells (Crispe and Bevan, 1987; Hunte et al., 1998; Liu et al., 1992; Rougon et al., 1991; Zhou et al., 1997). Dynamic regulation of CD24 expression was also observed in the nervous system (Calaora et al., 1996; Shirasawa et al., 1993), with expression in developing neurons (Calaora et al., 1996), astrocytes (Ennas et al., 1992), microglia(Bai et al., 2004), and a variety of cancer cells (Sanden et al., 2015), while being limited to regions of secondary neurogenesis in the adult central nervous system (CNS) (Calaora et al., 1996).

2. Molecular structure and post-translational modification of CD24

A cogent explanation of the diverse functions and signaling mechanisms attributed to CD24 (Table 1) will require an understanding of its molecular structure. The CD24 gene sequence is present in at least five locations of the human genome (chromosomes 1, 6, 15, 20 and Y). Sequence analysis suggests that CD24 mRNA is transcribed from the 6q21 locus, with the other homologous sequences acting as unexpressed pseudogenes, likely resulting from retrotransposition of the original sequence (Hough et al., 1994). The human CD24 gene encodes a transcript with a 0.24-kb open reading frame and a long 1.8-kb 3′ UTR (Wang et al., 2007). In mice, this unusually long UTR of CD24 has been shown to contain *cis* elements that regulate its mRNA stability (Zhou et al., 1998). Post-translation, the initial peptide is processed to remove the signal peptide, attach a glycosyl phosphatidylinositol (GPI) anchor, and incorporate specific glycan moieties. These modifications remove two-thirds of the original amino acids, resulting in a mature CD24 peptide of 32 residues in humans and 27 residues in the mouse ortholog (Kay et al., 1991). The protein core of human CD24 shares little consensus with the rodent forms, with most of the consensus occurring in the signal peptide and GPI anchor sequence.

Lacking a membrane-associating domain, CD24 is expressed at the cell surface via a GPI anchor. Consequently, CD24-mediated information is relayed to the cell interior through associated proteins for signal transduction, which may interact with CD24 on either the same cell (*cis*) or adjacent cells (*trans*) (see Fig. 1 and Fig. 2, respectively). Despite its small size, CD24 has many sites to accommodate its extensive glycosylation. The expected molecular weight of a mature CD24 peptide is approximately 3 kDa, but when isolated from tissue the apparent molecular weight ranges from 20 to 70 kDa, demonstrating the extent and variety of its glycosylation (Pearce et al., 1996; Rougon et al., 1991; Fang et al., 2010). Interactions between CD24 and its receptors likely depend on the glycoform expressed. Progress has been made to

Table 1
CD24 signaling.

Function	Effect	Cell system	References
MAPK signaling	↑ p38	Pre-B cell	Taguchi et al. (2003)
	↑ ERK1/2, Raf-1, p38	Colorectal cancer	Wang et al. (2010)
	↑ ERK1/2 (via ß1-integrin-FAK/Src)	Breast cancer	Lee et al. (2012)
	↑ Lyn (could mediate ERK/p38 activation)	Burkitt lymphoma cells	Suzuki et al. (2001)
	↑ Lyn-ERK1/2	Colorectal cancer	Su et al. (2012)
	↑ ERK1/2 & ↑ CXCR4	Cholangiocarcinoma	Leelawat et al. (2013)
	↑ SDF-1-CXCR4 signaling (potential role in ERK activity)	Breast cancer	Bajetto et al. (2001); Schabath et al., 2006
NF-κB signaling	↓ NF-κB	Human and mice after traumatic brain injury	Fukushima et al. (2007), Li et al. (2014)
	↓ NF-κB-DAMPS	Mouse dendritic cell	Chen et al. (2009)
Notch & Hedgehog signaling	↑ Notch 1	Hepatocellular carcinoma, breast cancer	Azzam et al. (2013), Lim et al. (2014), Wan et al. (2015)
	↓ STAT1-SHH	Breast cancer	Suyama et al. (2016)
	↑ Src-FAK (downstream regulation of STAT3)	Human tumor cell lines (lung adenocarcinoma, ovarian carcinoma, glioblastoma)	Bretz et al. (2012a, 2012b)
Other signaling networks	↑ TGF-ß3	hBMSC	Schäck et al. (2016)
	↑ EGFR and downstream PI3K/Akt & MEK/ERK pathway	Gastric cancer cells	Deng et al. (2016)
	↑ HER2-PI3K/Akt	Breast cancer cells	Hosonaga et al. (2014)
	↑ Src (downstream regulation of TFPI-2)	Human tumor cell lines (lung adenocarcinoma, ovarian carcinoma, glioblastoma)	Bretz et al. (2012a, 2012b)

↑: Upregulation; activation/ positive regulation.
↓: Downregulation; inhibition/negative regulation.