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Review

ShcC proteins: Brain aging and beyond

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ABSTRACT

To date, most studies of Shc family of signaling adaptor proteins have been focused on the near-ubiquitously expressed ShcA, indicating its relevance to age-related diseases and longevity. Although the role of the neuronal ShcC protein is much less investigated, accumulated evidence suggests its importance for neuroprotection against such aging-associated conditions as brain ischemia and oxidative stress. Here, we summarize more than decade of studies on the ShcC expression and function in normal brain, age-related brain pathologies and immune disorders with a focus on the interactions of ShcC with signaling proteins/pathways, and the possible implications of these interactions for changes associated with aging.

Contents

Abbreviations: Aβ, beta-amyloid; AD, Alzheimer's disease; Akt, protein kinase B (PKB); ALK, anaplastic lymphoma kinase (receptor tyrosine kinase); APP, alpha-amyloid precursor protein; ARDs, age-related diseases; AXL, receptor tyrosine kinase; BCR, B cell receptor; BDNF, brain-derived neuronal factor; CH1, collagen homology 1 domain; CNS, central nervous system; Crk, adaptor protein family; CS, cellular senescence; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; ERK1/2, extracellular signal-regulated kinases 1 and 2; Fyn, proto-oncogene non-receptor (soluble) tyrosine kinase; GAB1, Grb2-associated-binding protein 1; GDNF, glial-derived neurotropic factor; GluR, glutamate receptors (NMDA-type glutamate receptors); Grb2, growth factor receptor-bound protein 2; LPS, lipopolysaccharide; LTP, long-term potentiation; MAPK, mitogen-activated protein kinase; NGF, nerve growth factor; NGFR, nerve growth factor receptor; NMDA, *N*-methyl-D-aspartate; PD, Parkinson's disease; PI3K, phosphatidylinositide 3-kinase; PPI, protein–protein interaction; PTB, phosphotyrosine-binding domain; RAS, 'Rat sarcoma' signaling protein; RET, rearranged during transfection;receptor tyrosine kinase for glial cell line-derived neurotrophic factor (GDNF) family; RICS, Rho GTPase-activating protein 32; RNAi, RNA interference; ROS, reactive oxygen species; RTKs, receptor tyrosine kinases; SH2, Src homology 2 domain; Shc, Src homology and collagen homology; Src, 'Sarcoma' proto-oncogene non-receptor (soluble) tyrosine kinase; Syk, Spleen tyrosine kinase; TCR, T cell receptor; Trk, tropomyosin receptor kinase; ZAP-70, zeta-chain-associated protein kinase 70.

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1. Introduction

The Shc (Src homology and collagen homology) adaptor protein family has been extensively studied for more than two decades (reviewed by Wills and Jones, 2012). This family consists of four unique members, ShcA, B, C and D (Luzi et al., 2010; Hawley et al., 2011), and multiple splice isoforms that are involved in a wide repertoire of signal transduction events, mainly via phosphotyrosine-based interactions with a multitude of membrane receptors. While the flagship of the family, the almost ubiquitously expressed ShcA proteins, received most of the research attention (for review see: Luzi et al., 2000; Ravichandran, 2001; Wills and Jones, 2012) and were shown (especially $p66^{ShcA}$ isoform) to be involved in aging-associated pathology and in the control of lifespan (Migliaccio et al., 1999, 2006; Purdom and Chen, 2003; Sagi et al., 2005; Paneni and Cosentino, 2012; Diogo et al., 2013; Northey et al., 2013; Ranieri et al., 2013; Paneni et al., 2014), much more remains to be learned about the neuronal member ShcC. Here, we analyze the existing data on the biological functions of the ShcC with regard to aging, age-related diseases (ARDs) and conditions.

2. Structure, distribution and patterns of expression

The ShcC protein (Shc3, Rai, N-Shc, Shk) is expressed as two isoforms of 52 and 64 kDa, termed $p52^{ShcC}$ and $p64^{ShcC}$, respectively (Nakamura et al., 1996; O'Bryan et al., 1996; Pelicci et al., 1996). Similarly to the other members of the Shc family, the two ShcC isoforms have a unique PTB–CH1–SH2 modular organization, with two phosphotyrosine-binding domains, PTB and SH2 (Fig. 1).

The phosphotyrosine-binding (PTB) domain is found at the amino terminal, while the phosphotyrosine-binding Src homology 2 (SH2) domain is found at the carboxylic end (Pelicci et al., 1996). The CH1 (collagen homology 1) domain is located at the midst of the protein sequence. The PTB and SH2 domains confer binding to most of the defined ShcC partner proteins. The CH1 domain encompasses a proline-rich region that may bind SH3 domain-containing proteins and tyrosine residues that, upon phosphorylation, bind other SH2 domain-containing proteins (e.g. Grb2) (Luzi et al., 2000). The longer $p64^{ShcC}$ isoform has an additional amino-terminal CH2 region. The SH2 and PTB domains have relatively high homology to the corresponding domains of the other Shc proteins, ShcA and ShcB. However, even small structural differences in SH2 domains may be sufficient for ShcC-specific activity (O'Bryan et al., 1996). The central CH1 domain is less conserved and contains several ShcC-specific tyrosine residues which may stand behind unique ShcC/protein interactions and signaling.

While the expression of ShcA in the embryonic brain is absolutely essential for cell proliferation and normal development, the level of ShcC is low in the embryos but begins to increase around birth with a gradual rise during postnatal development, reaching peaks of expression in mature brain and spinal cord (Conti et al., 1997; Sakai et al., 2000; Ponti et al., 2005; Sagi et al., 2006). Thus, a switch from ShcA to ShcC expression parallels the decreasing proliferative processes in the developing brain. As a result, ShcC (along with ShcB) is the dominant family member in the post-mitotic and mature neurons (Ponti et al., 2005). In adult mice, the ShcC mRNA transcripts are abundant in the cerebrum, hippocampus, superior cervical ganglion (SCG), retinal ganglion cells and spinal cord (O'Bryan et al., 1996; Conti et al., 1997, 2001). Within the cells of the central nervous system (CNS), the ShcC protein is specifically localized to the neuronal cell bodies, main dendrites, and the nuclei of large-sized neurons (Ponti et al., 2005). ShcC is also expressed, albeit at lower levels, in enteric glial cells, endothelial cells, smooth muscle cells of the gastrointestinal tract, B and T lymphocytes, indicating functionality of this adaptor protein outside of the CNS (Villanacci et al., 2008; Savino et al., 2009).

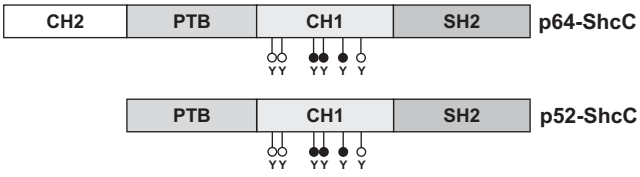

Fig. 1. Modular organization of ShcC isoforms. Y—tyrosine residuals in CH1 domain. Black circles—tyrosine residuals that are specific for ShcC. For details, see Section 2.

Remarkably, ShcC as well as other neuronal members of Shc family (ShcB and ShcD) appear much later in evolution than ShcA. Their appearance is clearly associated with evolution of CNS in vertebrates. Indeed, using the InParanoid database (Ostlund et al., 2010; http://inparanoid.sbc.su.se/), we conducted a comprehensive evolutionary conservation analysis of Shc proteins, covering 273 eukaryotic species, and found that the ShcB, ShcC and ShcD members appear only in vertebrates, starting from the primitive fish—the lampreys (*Petromyzontiformes*), while the ShcA is present in all classes of Metazoa. The origin of the ShcC in evolution is also close to the origin of the adaptive immune system (Flajnik and Kasahara, 2010). Our findings are in line with the results of multiple sequence alignments analysis carried out by Luzi et al. (2000) for three mammalian species (*Homo sapiens*, *Mus musculus* and *Rattus norvegicus*), fish *Fugu rubripes*, the insect *Drosophila melanogaster*, and nematode *Caenhorabditis elegans*, who showed that the Shc protein family has undergone diversification and an increase in complexity during the evolution.

3. Interacting partners

ShcC acts as adaptor protein coupling signals from multiple receptors with tyrosine kinase activity to downstream signaling pathways associated with maturation and survival of neurons. As such, its activities in the brain are carried through interactions with the first-order protein partners. While the protein–protein interactions (PPIs) of the ShcA have been studied extensively, only several PPIs of ShcC have thus far been described (Fig. 2). For example, ShcC was found to interact with several growth factor receptors with tyrosine kinase activity such as RET (Pelicci et al., 2002; De Falco et al., 2005), TrkA (nerve growth factor receptor, NGFR), TrkB (receptor for brain-derived neuronal factor, BDNF) (Nakamura et al., 1996, 2002; Liu and Meakin, 2002) and EGFR/ErbB1 (epidermal growth factor receptor) (O'Bryan et al., 1996, 1998; Nakamura et al., 2002).

The ShcC PPIs might be isoform specific. For example, in primary neuronal cultures established from dorsal root ganglia of adult rat, only the "short" isoform of ShcC ($p52^{ShcC}$) was phosphorylated in response to NGF, while EGF caused phosphorylation of both ShcC isoforms (Ganju et al., 1998). ShcC binding to activated receptors results in phosphorylation of tyrosine residues within ShcC CH1 central domain and allows ShcC binding to Grb2 and other adaptor proteins, thus initiating downstream signaling through PI3K/Akt and RAS/MAPK pathways that control neuronal survival and differentiation, respectively (Conti et al., 2001; Liu and Meakin, 2002; Pelicci et al., 2002; Troglio et al., 2004). Although the efficiency of ShcC in triggering the Ras/MAPK signaling is significantly lower than that of ShcA (Nakamura et al., 2002), activation of the Ras/MAPK pathway by ShcC is important for regulation of long-term potentiation (LTP), one of the major mechanisms underlying synaptic plasticity and thereby learning and memory (Nakamura et al., 1996, 2002; Liu and Meakin, 2002; Petralia et al., 2014) (see also Section 4.3).