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Short Communication

The Multiple Mechanisms of Anti-Tumor function of Calcineurin B Subunit

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Abstract

Calcineurin B subunit (CnB), the regulatory subunit of calcineurin (Cn), has been reported to have an anti-tumor function. In recent years, researchers are gradually unveiling the possible mechanisms of the tumoricidal function of CnB. These proposed mechanisms can be divided into two categories: immunity-mediated killing and direct pro-apoptotic killing. In this short communication, we discuss these distinct but related underlying mechanisms of the CnB-mediated anti-tumor function.

Keywords: Calcineurin; Calcineurin B Subunit; Anti-Tumor; Immunity-Mediated Killing; Pro-Apoptotic Killing

Calcineurin (Cn) is the only known Ca^{2+}/calmodulin-dependent serine/threonine protein phosphatase; it is a heterodimer composed of a 61-kDa catalytic subunit (CnA) and a 19-kDa regulatory subunit (CnB) [1]. This enzyme, expressed in various cell types, plays an important role in modulation of T-cell activation [2], neural functions [3], apoptosis [4], and cardiac hypertrophy [5]. Traditionally, the role of CnB was thought to regulate the phosphatase activity of CnA. However, in recent years, new studies suggest CnB is not only an adjuvant protein as the regulatory subunit of Cn, but also has a role in anti-tumor activity. In the last decade, researchers have discovered anti-tumor function of CnB. One study showed that intraperitoneal injection of CnB protein can prolong the survival of mice bearing H22 ascites tumors and inhibit the growth of S180 sarcomas in mice [6]. Moreover, scientists are gradually unveiling the underlying mechanisms of the tumoricidal function of CnB. Some of the proposed mechanisms fall into one of two categories: immunity-mediated killing and direct pro-apoptotic killing.

Immunity-Mediated Tumor Killing

CnB stimulates dendritic cell maturation and activation and enhances antigen presentation. This function of CnB has been utilized for the development of novel adjuvant for both cancer vaccine [7] and the Engerix-B HBV vaccine [8]. Studies show that CnB can bind to the transmembrane receptor integrin αM on macrophages and induce TNF-related apoptosis-inducing ligand (TRAIL) expression *in* vitro and in vivo [9,10]. TRAIL, a member of the TNF family of cytokines, triggers apoptosis of a variety of tumor cells by engaging the death receptors DR4 and DR5, despite displaying no cytotoxicity against most normal cells [11]. The tumoricidal activity of CnB-activated peritoneal macrophages has been shown to be partially dependent on TRAIL [9]. Interestingly, CnB may assist IFN-γ to make macrophages highly cytotoxic to cancer cells. More specifically, CnB and IFN-γ act synergistically to polarize mouse tumor-associated macrophages, as well as human monocyte-derived macrophages

to an M1-like phenotype [12]. Macrophage polarization to M1-like phenotype has been reported to enhance the anti-tumor immune response [13]. Mechanistically, the synergy between CnB and IFN-γ is mediated by the crosstalk between CnB-engaged integrin αM-p38 MAPK signaling and IFN-γ-initiated p38/PKC-δ/Jak2 signaling. These two pathways eventually converge to the common molecular signal transducer and activator of transcription 1 (STAT1) and lead to greater production of anti-tumor molecules [12]. In addition, CnB can also interact with Toll-like receptor 4 and increase interferon-β production, which may also contribute to its tumor eradiation function [14].

Direct Pro-Apoptotic Killing

Saeki et al. reported that CnB can bind with procaspase-3 to potentiate its activation by accelerating its proteolytic maturation. Overexpression of CnB promoted the processing of caspase-3 and TNF-and-cycloheximide-induced apoptosis [15]. Cheng et al. found that overexpression of CnB increased intracellular Ca^{2+} concentration, enhanced caspase-3 activity, decreased Bcl-2 expression, and lowered mitochondrial membrane potential. Notably, CnB can bind to isolated mitochondria in a Ca^{2+}-dependent manner and subsequently promote cytochrome c release from the mitochondria. Further study revealed that CnB may interact with a pro-apoptotic mitochondrial protein Bcl-B. These findings suggest that CnB may enhance TNF-induced apoptosis, possibly by acting on mitochondrial functions [16]. Additionally, Li et al. reported that CnB may interact with the heat shock protein 60 (Hsp60) in a Ca^{2+}-dependent manner [17]. Although the authors did not show the biological function of this interaction, numerous studies have revealed the role of Hsp60 in apoptosis. Therefore, the interplay between CnB and Hsp60 in regulation of apoptosis is possible and under investigation.

In addition to the mechanisms of immunity-mediated tumor killing and direct pro-apoptotic killing, CnB, with the interaction with proteasome subunit alpha type 7 (PSMA7), was also shown to repress the expression of vascular endothelial growth factor (VEGF) by modulating the proteasome pathway [18]. The major interacting proteins of CnB are diagramed in Figure 1.

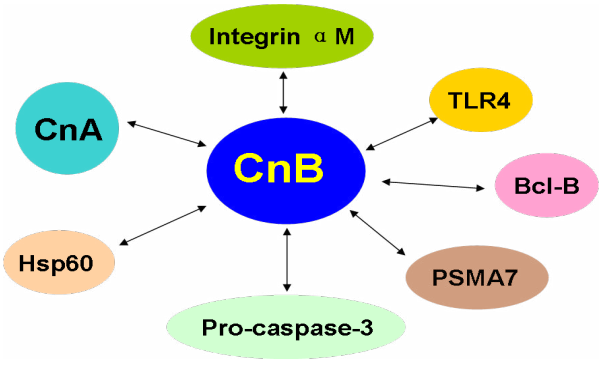

Figure 1. The major interacting proteins of CnB.

As discussed above, the proposed mechanisms of the anti-tumor function of CnB are multifaceted and complex. Future studies will identify and characterize the dominating mechanism(s) for distinct tumor cell types in different microenvironments.

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