The 14-3-3 Proteins and Their Function in Intestine

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Abstract

The 14-3-3 family proteins exert their functions by interacting with their target proteins. In the intestine cells, 14-3-3 family proteins participate many critical signaling cascades governing cell differentiation, survival, apoptosis and polarity. The expression levels of 14-3-3 family proteins were mis-regulated in most colorectal cancers, and thus they may serve as progonostic biomarker for colorectal cancers. The 14-3-3 proteins may also have roles in protecting intestine cells from radiation exposure and parasites infection. Overall, the 14-3-3 family proteins play multiple roles in intestine and are critical in maintaining intestine health.

Introduction

The 14-3-3 family proteins were first described in 1967 in the process of systematic classification of nervous tissue proteins [1]. By separating the homogeneous sample of brain tissue using reverse phase high-pressure liguid chromatography (HPLC), seven isoforms of 14-3-3 were characterized: β, ε, η, γ, τ (also called θ), ζ and σ. The name "14-3-3" reflects the fraction number enriched in these proteins on ion-exchange chromatography of bovine brain extract and the position of these proteins on starch gel electrophoresis. The 14-3-3 proteins have low pI value (4.0-4.5) and the molecular mass of the 14-3-3 monomer is close to 30 kDa [2]. These proteins are widely expressed in human tissue, with particular high content in brain, testis, and intestine (>0.5% of all soluble proteins) [3].

The 14-3-3 proteins are small scaffold proteins, which bind to their target proteins through the conserved binding motifs. Phosphorylated Ser (pS) or Thr (pT) residues in RSXpSXP or RXXXp(S/T) XP motifs are well-known common 14-3-3-binding sites [4]. Upon binding, 14-3-3 proteins may change the activity or the localization of the target proteins and thus to regulate the cellular functions. At present, there are more than 300 14-3-3 interacting targets described in the literature [5, 6]. By interacting with their targets, the 14-3-3 family proteins participate in a variety cellular functions, including apoptosis, cell cycle, proliferation, transcription, replication, and organization of cytoskeleton. In the intestine, these proteins are highly expressed, especially with the isoforms of ε, η αvδ ζ [7, 8]. Not only do these proteins participate in the signaling cascade in intestine epithelial cells, their misregulation also has important contributions in disease in the intestine.

The Function of 14-3-3 Proteins in Signal Transduction

The mammalian intestine is covered by a single layer of epithelial cells that is renewed in every 4-5 days. This renewal is achieved by the intestine stem cells that reside in the crypts of the intestine. The stem cells make progenitor cells and then the progenitor cells differentiate along with upward migration to reach the tip of the villus and then go apoptosis. Multiple signaling pathways are involved here for the epithelial cells proliferation and apoptosis. Among them, the BMP (bone morphogenetic protein) signal, Akt/PI3K signal and Wnt/β-catenin signal are probably the most fundamental ones [9-12]. Using genetic targeting of BMP1A in mice, researchers found that inactivation of BMP signaling results in multiple polyps due to an increased number of crypts and stem cells, accompanied by enhanced Wnt signaling in all proliferative intestine cells. They also found that 14-3–3ζ exists in the β–catenin complex and facilitates activation of b-catenin by Akt [13]. In colon cancer cells, 14-3-3 proteins may participate in the regulation of NF-κB signaling by binding to the N-Cor protein and resulting its aberrant cellular localization [14]. In aging rat model, decreased apoptosis and increased survival of cells in the colonic mucosa were observed. Akt phosphorylates the pro-apoptotic

protein Bad, resulting in a reduction in nonphophorylated Bad. 14-3-3 family of proteins sequesters the phosphorylated bad protein and preventing its apoptotic function in mitochondria [15].

Besides the functions of regulating on the proliferation and apoptosis in intestine cells, 14-3-3 proteins also have many functions in modulating cytoskeleton and establishing cell polarity. In the mammalian intestine, the differentiated epithelial cells display strong apical-basal polarity with a highly developed F-actin-rich brush border in the apical plasma membrane of absorptive epithelial cells. The 14-3-3 family proteins interact with polarity establishing protein Par3α and Par3β in a phosphorylation dependent manner [16]. In the intestine of C. elegans, 14-3-3 proteins located in the Rab11-positive recycling endosomes, an important structure for establishing and maintaining epithelial polarity in intestine [17] 14-3-3 family proteins may also participate in regulation of actin dynamics by interacting with Cofilin, and protecting actin from cofilin-induced fragmentation [18, 19]. Multiple evidences showed that 14-3-3 family proteins are also able to regulate cytoskeleton dynamics by modulating Myosin assembly dynamics [20-24]. In Dictyostelium cells, 14-3-3 is required for promoting myosin II bipolar thick filament remodeling [25].

The role of the 14-3-3 family proteins in health, disease, and drug development 14-3-3 family proteins were initially discovered in brain tissue and were considered to have high correlation with neurodegenerative diseases [26, 27]. More recently, the levels of 14-3-3 proteins were also found to be abnormal in different types of cancer [28-30]. All these data suggest that 14-3-3 maybe a perspective marker for human diseases.

In the effort of searching for protein expression level change between normal colon tissue and colonic polyps, the level of 14-3-3σ was increased significantly, suggesting that the signaling cascade associated with this protein is mis-regulated in colonic polyps and this protein may also serve as a biomarker for colon

cancer classification [31]. In a separated study of searching for colorectal cancer's prognostic biomarkers, 14-3-3β was identified as an ideal biomarker after studying the proteins expression level between normal colon tissues and colon cancer tissues [32]. More interestingly, the nuclear fraction of 14-3-3ε may serve as a suppressor of tumor metastasis. Loss of nuclear 14-3-3ε is closely associated with poor overall survival in colorectal cancer patients, which suggests that nuclear 14-3-3ε may serve as an important biomarker of tumor metastasis [33]. Other than the above-mentioned 14-3-3 isoforms, the expression level of 14-3-3 ζ/δ was found misregulated as well in colorectal cancer tissue [34]. In the case of pancreatic adenocarcinomas, the promoter region of 14-3-3σ was found to be hypomethylated, leading to overexpression of this protein in poorly differentiated cancers. And the expression amount was associated with survival rate of these patients [35].

Other than serving as the cancer biomarkers, 14-3-3 family proteins also participate in many other functions in intestine health. For example, in the study of the protective mechanism of amifostine on intestine after radiation exposure, 14-3-3σ was found to interact with p53 and induce p53's tetramerization in the nucleus that rescue lethal small bowel damages by radiation exposure [36]. In the example of parasite infection by Toxoplasma gondii, 14-3-3 may have protective roles for cell survival and prevention of parasite replication [37-39].

In a summary, 14-3-3 family proteins participate in many critical signal transduction pathways in intestine cells, governing intestine epithelial cells differentiation, survival and apoptosis. 14-3-3 also serves many roles in establishing and maintaining the polarity of the intestine epithelial cells, as well as regulating cytoskeleton dynamics by interacting actin associating proteins and myosin filaments. In the study of colorectal cancer, many 14-3-3 family proteins were identified as perspective prognostic biomarkers. And at last, 14-3-3 family proteins were also associated with intestine cells survival after radiation exposure and parasites infection.

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