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Letter to the Editor

RSK-dependent 14-3-3 interactions

Sir,

14-3-3 proteins were identified as abundant proteins from bovine brain homogenates. They eluted at the 14th fraction from a two-dimensional DEAE-cellulose chromatography column and were the 3.3 band on the subsequent gel electrophoresis.[1] 14-3-3s were also given different names according to their novel roles in different organisms ranging from plants to animals as reviewed by Aitken.[2] Physiologically, these are 30kDa acidic proteins and modulate other proteins in signal transduction pathways by binding to specific phospho-serine/threonine target motifs. The two highly preferred motifs recognized by 14-3-3 on their target proteins are R[S/Φ][+]pS/TXP (mode 1) and RX[S/Φ][+]pS/TXP (mode 2) where pS/T means phosphorylated serine or threonine, Φ means an aromatic residue, + is a basic residue and X is any type of an amino acid with a preference for Leu, Glu, Ala, Met.[3] The regulation of multiple oncogenic proteins has spotlighted 14-3-3 as the central point of various signaling cues which govern cell proliferation, growth and tumor suppression.[4] There are seven distinct isoforms in mammals (ζ, β, γ, η, σ, τ and ε), fifteen in plants and two each in D. melanogaster and C. elegans.[5] They exist as homodimers and except for the sigma isoform which exists as heterodimers within the cell and can bind to more than one protein due to the dimerization of the monomers.[12]

The RAS-Mitogen–activated protein kinase (MAPK) pathway is a key signaling pathway crucial for the regulation of normal cellular proliferation, survival, growth and differentiation. This important pathway has been the focal point of extensive research because of the activating mutations occurring in the many signaling components of this pathway which are hallmarks of several human cancers and neurodegenerative diseases. The 90kDa ribosomal S6 kinases (RSKs) are a family of serine/threonine kinases that are activated downstream of the RAS-MAPK pathway.[13]

In humans, this family of kinases consists of four isoforms (RSK1-4) sharing high sequence homology. The RSK isoforms are directly activated by extracellular-signal regulated kinase 1 and -2 (ERK1/2) in response to growth factors, phorbol esters, neurotransmitters, chemokines and other external stimuli. RSKs phosphorylate many cytosolic and nuclear targets. These phosphorylation events are involved in various significant cellular processes.[6] This editorial extends our understanding of how 14-3-3 proteins and RSK kinases can coordinate and regulate their common target proteins.

Well-known RSK–regulated 14-3-3 interactions

RSK can be localized into various subcellular compartments including the plasma membrane, the cytosol or the nucleus, where it finds different target proteins in these cellular compartments. RSK phosphorylates its targets at serines and very rarely threonines in the RXXS motifs which completely overlaps the 14-3-3 binding sequence motifs.[7] Various RSK substrates are well known to bind to 14-3-3 via its RSK phosphorylated residues like SOS1, PDCD4, BAD.[7-9]

Physiological importance of RSK-14-3-3 interaction

The impact of the RAS-MAPK pathway in a variety of human cancers is evident due to activating mutations of K, N, H –RAS and A, B and C-RAF (RAF-1) proteins. About 20% of human cancers contain activating point mutations in RAS and RAF proteins, therefore making them target proteins for inhibiting malignant. Targeting mutant RAS proteins with the help of small molecule inhibitors have failed to reduce malignancies so far. It is evident that the RAS-MAPK pathway can also get activated without the involvement of RAS protein.

Mutated RAF proteins are also a major cause for cancers and are resistant to pharmacological inhibitors which directly targets RAS because RAF becomes constitutively active in these mutated cancerous cells, bypassing RAS activation. Now the focal point for targeting cancers has shifted to proteins which are activated downstream of the RAS-MAPK pathway. We could target other proteins like RSK in the RAS-MAPK pathway. The advantage of targeting RSK in RAF mutated cancers is, RSK-dependent negative regulation of SOS1 is non- functional in RAF- mutated cancers.[8] Therefore, RSK inhibitors can be used to block proliferative functions of RSK. The disadvantage of targeting RSK in all cancers will be to inhibit negative regulation of RSK in the RAS-MAPK pathway, if the activating mutations are in RAS or EGFR.

RSK inhibitors- RSK inhibitors like SL0101 and BI-D1870 have shown anti-proliferative potency. When RAF-1 is constitutively active and resistant to RAF-1 inhibitors, then dosage dependent cocktail of RAF and RSK inhibitors could be used to suppresses proliferative tendencies of a tumor.[10]

The high levels of 14-3-3 protein expression in colon and pancreatic cancers have implicated 14-3-3 as potential biomarkers for cancers.[11] However, 14-3-3 has been

found to be both upregulated and downregulated in different tumors. This brought into question the involvement of 14-3-3 in the RAS-MAPK pathway as general negative regulators. We have to identify mutated proteins present in different tumors to understand how tumor proliferation can be prevented. As mentioned earlier, RAF mutated tumors will not respond to RAS or EGFR inhibitors. These tumors are resistant to RAS and EGFR inhibitors because they have bypassed EGFR and RAS activations. Colon and pancreatic tumors were reported to have the most RAF mutations and 14-3-3s were found to be upregulated in these tumors, which suggests that although 14-3-3 could negatively regulate RAF in a normal cell, the colon and pancreatic tumors are resistant to negative regulatory functions of 14-3-3.[4] While the cause for the upregulation of 14-3-3 is still elusive in such tumors, these scenarios highlight that 14-3-3 might play a role in promoting cell proliferation and survival through binding to an unknown protein or proteins. Therefore the role of 14-3-3 in human cancers can be a double-edged sword.

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