The mysteries of S6K2 may shed light to breast cancer therapy path.

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Abstract

The divergence between S6 Kinase 2 (S6K2) and its homologue S6 Kinase 1 (S6K1) has displayed that the exclusive functions of S6K2 are very important mediators of tumor growth. Recent studies suggest that S6K2 complexes with B-Raf and PKCε to exert cancer cell survival. Also, indirect roles of S6K2 which involve interaction with Akt and PDCD4 to propagate cancer cell survival make it an important therapeutic target. Also, centrosomal localization of a pool of S6K2 potentiates a proliferative role. Amplification and overexpression of RPS6KB2 gene locus, which encodes S6K2 protein, is observed in breast cancer and is correlated with poor prognosis. Also, S6K2 expression is correlated with 4EBP1 and E2F1 expression in breast cancer. Also, breast cancer tissues display nuclear over-accumulation of S6K2 when compared to its normal counterparts. Currently, the mechanisms which regulate the cellular levels of S6K2 are unknown. Also, there still remains new substrates of S6K2 to be unraveled. As the mysteries of S6K2 is solved, new stones are paved in the breast cancer therapy path.

Keywords: S6 Kinase 2, Breast cancer, Cancer therapy.

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Introduction

S6 Kinase family proteins are very important downstream effectors of PI3K/Akt/mTOR signaling pathway. S6K2, as the younger member of S6 Kinase family, has recently gained remarkable attention as its substrates continuously diverge from that of S6K1, the older member of S6 Kinase family. It has two isoforms: p54 and p56. p56 mainly localizes in nucleus whereas p54 displays both nuclear and cytoplasmic localization. Their only common substrates are S6 and PDCD4. S6K1 and S6K2 phosphorylate different substrates and therefore play important roles in cell growth, proliferation, survival and metabolism.

Although most of the structures and the activation patterns of S6K1 and S6K2 are quite similar, recent studies have uncovered exclusive roles for S6K2. The presence of proline-rich domain in S6K2 enlarges its repertoire of substrates, several of which are still unknown [1-3].

The studies in the last two decades have unraveled the link between S6K2 and cancer. Two studies by Pardo et al. [4,5] displayed that S6K2 both induced proliferation and evaded apoptosis in FGF-2 induced small cell lung cancer (SCLC) cells. A very recent study from Amaral et al. [6] unraveled that S6K2 promoted cell survival, migration and tumorigenesis in PC3 prostate cancer cell line.

Moreover, more abundant number of studies came from breast cancer. We aim to review the recent breakthroughs that explores the role of S6K2 in breast cancer and to shed light to putative therapeutic approaches.

S6K2 and Breast Cancer

A Ukranian research group examined the expression pattern of S6K2 in breast cancer in early 2000s. They discovered the overexpression of S6K2 in breast cancer tissues when compared to their normal counterparts [7]. In normal breast tissues, S6K2 tended to localize in the cytoplasm whereas it displayed more nuclear pattern in breast cancer tissues [8].

S6K2 expression also displayed positive correlation with PCNA and Ki-67 expression. This might suggest that S6K2 is involved in breast cancer cell proliferation [9]. These characteristics were not observed for S6K1.

A Swedish research group investigated the relationship between S6K2 and breast cancer survival last decade. An earlier study unraveled the amplification of S6K2-encoding RPS6KB2 gene in breast cancer tissues [10]. Positive correlation of S6K2 expression with 4EBP1, another mTOR effector protein which promotes protein translation thus cell growth, was observed in breast tumor tissues from postmenapousal women. Also, higher expression of S6K2 and 4EBP1 yielded lower survival of these women [11]. In both studies, it was displayed that the ER/PgR subgroups and the subcellular localization of both S6K2 and 4EBP1 defined important prognostic values in response to tamoxifen treatment. More cytoplasmic 4EBP1 localization predicted a worse outcome in ER+/PgR+ breast cancer subgroup when treated with tamoxifen. On the other hand, nuclear S6K2 predicted a better outcome in ER+/PgR+ subgroup, but a worse outcome in ER+/PgR- subgroup in breast cancer cohorts in response to tamoxifen treatment [10,11]. Another study by the same group investigated the correlation patterns of S6K1-, S6K2- and 4EBP1-expressing breast tumors with other genes. Interestingly, the correlation between S6K2 and 4EBP1 is much more prominent than these two proteins with S6K1

separately. S6K2 and 4EBP1 displayed very high correlation with cell cycle associated genes, especially with E2F1 and CCNB1 [12].

Two studies by Sridharan and Basu discovered how S6K2 contributed to cancer cell survival in breast cancer cell lines. They found out that downregulation of S6K2 yielded an increase in TNF-induced apoptosis in MCF-7 cells. This induction of apoptosis was overturned by Akt overexpression, pointing out that a positive feedback mechanism of Akt activation by S6K2 is involved in breast cancer cell survival, on the contrary that Akt is negatively regulated by S6K1. Bid, a pro-apoptotic protein was also shown to be interfered by S6K2 to maintain breast cancer cell survival [13]. A more recent study by the same group displayed that Mcl-1, an anti-apoptotic protein, was regulated by S6K2 to maintain survival in T47D cells. This effect was partly blocked by JNK1, suggesting that S6K2 activated Mcl-1 partly via deactivating JNK1 [14].

Conclusion

The aforementioned studies in this review, exploring the role of S6K2 in breast cancer, have demonstrated that S6K2 might have a great potential in targeted therapy in breast cancer. As long as the new interacting partners and substrates of S6K2 are uncovered, more targeted approaches of S6K2 interactions will be under spotlight.

Future Perspectives

- There still remains several questions to be answered for S6K2. As long as the mysteries of S6K2 are solved, new paths for breast cancer therapy will be opened.
- The proline-rich domain found in S6K2 prompts that there are several substrates with which S6K2 might be interacting and which are still unknown.
- The mechanisms which regulate S6K2 cellular steady-state level are not completely known.
- The microRNAs which regulate cellular S6K2 level are unknown. The only discovered microRNA is miR-193a-3p.
- The E3 ubiquitin ligase and DUB enzyme for S6K2 are currently unknown.
- There is no current S6K2-specific inhibitor. Its development might direct breast cancer cells to apoptosis and loss of chemotherapy resistance [15].

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