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THE ROLE OF S6K1 ISOFORMS IN REGULATING ESR1 PHOSPHORYLATION AT SER118 AND SER167 SITES CRUCIAL FOR ITS ACTIVITY, AND THE RECIPROCAL EFFECT ON S6K1 ACTIVITY

Crosstalk between S6K1 kinase and estrogen receptor alpha (ESR1) represents one of the key mechanisms driving the breast cancer cell growth, survival, and hormone resistance. S6K1 directly regulates ESR1 activity through Ser167 phosphorylation. Consequently, the receptor becomes activated and stimulates the transcription of target genes even in the absence of estrogen or when the receptor is blocked. Conversely, estrogen, upon binding to ESR1, enhances the transcription of mTOR pathway components and the RPS6KB1 gene itself. Thus, the functional interaction between S6K1 and ESR1 integrates signals from growth factors and steroid hormones, and a high expression level or hyperactivity of S6K1 in patients with ER⁺ breast cancer often correlates with a poor prognosis. **Aim.** To investigate the role of specific S6K1 isoforms in regulating ESR1 phosphorylation at sites crucial for its activity – Ser118 and Ser167 – and simultaneously to elucidate its role in regulating the activity of S6K1 itself. **Methods.** Site-directed mutagenesis of the ESR1 gene. Generation of stable MCF-7 cell lines with differential expression of S6K1 isoforms (p60, p70, and p85) and expression mutant ESR1 forms. Western blot analysis of ESR1 phosphorylation at Ser167 and Ser118. **Results.** The role of S6K1 isoforms in regulating ESR1 phosphorylation at its key functional sites, Ser118 and Ser167, was determined. MCF-7 model cells with differential expression of S6K1 isoforms were utilized. It was established that expression of p70/S6K1 or p60/S6K1 correlates with a 3- and 5-fold increase, respectively, in ESR1 phosphorylation at Ser167 compared to cells with knockdown of all isoforms. In contrast, upon p85/S6K1 expression, the level of ESR1 phosphorylation at this site remains unchanged. Analysis of ESR1 phosphorylation at Ser118 indicates a 5-fold increase upon expression of p85/S6K1, unlike with p70/S6K1 and p60/S6K1. Using mutant MCF-7 sublines with a ESR1 phosphorylation site mimicry (Ser167Asp) and a phosphorylation site blockade (Ser167Ala), it was established that ESR1 phosphorylation exerts no regulatory effect on S6K1 activity. **Conclusions.** The results indicate distinct roles of S6K1 isoforms in ESR1 phosphorylation at sites crucial for its activity, while simultaneously demonstrating the absence of a reciprocal relationship between ESR1 phosphorylation at Ser167 and the regulation of S6K1 activity. **Funding.** This work was supported by the National Research Foundation of Ukraine (Ref. 2023.03/0120).

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