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The p52 isoform of *Shc1* is a key driver of Breast Cancer initiation

Andrey Sorokin
Medical College of Wisconsin, USA

Family of Shc adaptor proteins (encoded by Shc1 gene) consists of three functionally distinct isoforms (p46Shc, p52Shc, and p66Shc) that serve as intracellular adaptors for several key signaling pathways in breast cancer. Despite the broad evidence implicating Shc1 as a central mediator of breast cancer, testing the isoform-specific roles of Shc1 have been inaccessible due to the lack of isoform-specific inhibitors or gene knockout models. Here, we addressed this issue by generating the first isoform-specific gene knockout models for p52Shc and p66Shc, using germline gene-editing in the SS rat strain. Compared with the wild type (WT) rats, we found that genetic ablation of the p52Shc isoform significantly attenuated mammary tumor formation, whereas the p66Shc knockout had no effect. These data, combined with p52Shc being the predominant isoform that is upregulated in human and rat tumors, provide the first evidence that p52Shc is the oncogenic isoform of Shc1 in breast cancer. Compared with WT tumors, 893 differentially expressed genes were detected in p52Shc KO tumors compared with only 18 differentially expressed genes in the p66Shc KO tumors, further highlighting that p52Shc is the relevant Shc1 isoform in breast cancer. Finally, gene network analysis revealed that p52Shc KO disrupted multiple key pathways that have been previously implicated in breast cancer initiation and progression, including ESR1, mTORC2/RICTOR, and STAT5. Collectively, these data demonstrate the p52Shc isoform is the key driver of DMBA-induced breast cancer while the expression of p66Shc and p46Shc are not enough to compensate.

e: sorokin@mcw.edu

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