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## Interplay between Mevalonate and Hippo pathways regulates DDX20 transcription via YAP-TEAD complex in triple negative breast cancer

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Statins, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors are commonly used drugs for the treatment of hypercholesterolemia. Moreover, increasing preclinical and clinical evidence suggests that statins may also play a potential role in the treatment of cancers, including breast cancers. Specifically, statins have been shown to exert several beneficial anti-neoplastic properties, including decreased tumor growth, angiogenesis and metastasis. DEAD-box RNA helicases are a family of proteins that have been widely studied for their roles in RNA metabolism and have lately been implicated in cancers. DDX20, a member of this family was recently reported by our group as a novel metastasis-promoting oncogene in Triple Negative Breast Cancer (TNBC), suggesting that its expression levels may serve as a biomarker for drug effectiveness. A correlation between genes of the mevalonate pathway and DDX20 expression assessed in a cohort of breast cancer patients showed a highest positive correlation with expression of HMG CoA reductase. Herein, we investigated if expression levels of DDX20 can be used clinically as a surrogate marker for simvastatin response. Collectively, our *in vitro* and *in vivo* studies clearly demonstrated that high DDX20 expressing TNBC cells are more responsive to simvastatin exposure as compared to lower DDX20 expressing luminal cancer cells. Indeed, exposure of TNBC cells to statins decreases expression of DDX20 in a cholesterol-independent but mevalonate pathway-dependent manner via inhibition of RhoA. Similar activity was observed by evaluating expression of DDX20 protein levels in pre- and post-simvastatin tumor biopsies in newly diagnosed primary breast cancer patients. Interestingly, a recent study reported the mevalonate pathway via RhoA regulates YAP/TAZ, a key effector of Hippo pathway, and it prompted us to uncover an interesting interplay between DDX20 and YAP-TEAD complex in TNBC.

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