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DEAD-BOX RNA HELICASE DP103 ENHANCES YAP SUMOYLATION FOR YAP-TEAD DEPENDENCE AND STATIN SENSITIVITY IN TRIPLE NEGATIVE BREAST CANCER

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Simvastatin, a lipophilic statin used for lowering cholesterol, inhibits 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR), the key enzyme of the mevalonate pathway. Studies have shown that cancer cells express deregulated level of HMGCR and statins exert anti-tumoral activities. We first assessed correlation between mevalonate pathway genes and DDX20 (DP103, Gemin-3) in 1325 breast cancer patients and observed a positive correlation between DDX20 and the mevalonate pathway genes. Having this data, we then proceeded to explore the effect of statins on DDX20 expression. We used various *in vitro* cell lines and *in vivo* statin clinical trial patients' specimens, mouse xenograft, mouse intravenous tail injection and *Drosophila* (wild-type vs Gemin-3 knockdown vs Gemin-3 overexpression flies) models. We show exposure to statin decreases the expression of DDX20. Through a series of add-back experiments, we show that the decrease in DDX20 expression by statins is via the mevalonate pathway and downstream of RhoA. In clinical specimens, we observed breast cancer patients with high baseline DDX20 positively correlates with high baseline YAP-TEAD expression. Having known that SUMOylation of YAP maintains its activity and that DDX20 is a critical enhancer of the SUMOylation machinery, we showed through a series of experiments that a physical interaction between DDX20 and YAP is crucial for maintaining SUMOylation of YAP; thereby decreasing its ubiquitination and degradation. Interestingly, we also identified for the first time that DDX20 is a direct target of YAP-TEAD complex and that maintenance of DDX20 expression is needed as a positive feedback forming an Achilles heel for sustained YAP-TEAD activity.

BIOGRAPHY

Alan Prem Kumar has completed PhD from University of North Texas, USA. He is currently an Assistant Professor at the National University of Singapore. He has over 150 publications that and his publication H-index is 36 and has been serving as an editorial board member of reputed Journals and established several industry collaborations.

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