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TIP60 inhibits epithelial-mesenchymal transition program in breast cancer: A HAT with many tricks

HIV-Tat-interacting protein 60 KDa (TIP60) is a lysine acetyltransferase implicated in transcription, DNA damage response and apoptosis. It is known to be downregulated in multiple cancers. Recent studies have shown that TIP60 downregulation correlates with node positivity, metastasis and poor survival rate. Epithelial-mesenchymal transition (EMT) is considered as an important step in cancer metastasis. During this process, there is an overexpression of EMT inducers such as Snail2 (also known as Slug) and repression of cell adhesion molecules such as E-cadherin and EpCAM. Additionally, previous report has demonstrated that E-cadherin and EpCAM expression were repressed by DNA hypermethylation on their promoter region during EMT. In this conference, I will be discussing data that show TIP60 expression partially abrogates cell migration and metastatic potential of breast cancer cells both in vitro and in vivo models. Mechanistically, we show this is through its ability to destabilize DNMT1 and inhibit Snail2 expression. Depletion of TIP60 stabilizes DNMT1 and increase Snail2 level, resulting in the EMT. Activation of DNMT1-Snail2 axis in the absence of TIP60 represses expression of epithelial markers by increased DNA methylation on their promoter region. In pathophysiological scenario, we find TIP60 to be significantly down-regulated in breast cancer patients with poor Overall Survival (OS) and Disease-Free Survival (DFS) prognoses. These data suggest that levels of TIP60 can be a prognostic marker of disease progression and stabilization of TIP60 could be a promising strategy to treat cancers.

Biography

Sudhakar Jha's group is interested in understanding the regulation of chromatin remodeling complexes and their role in cancer prevention and intervention. Chromatin remodeling complexes play an important role in maintaining chromatin organization as they create a histone code that is read by specific readers resulting in an active or repressed chromatin. Dr. Jha's group has purified and characterized chromatin-remodeling complexes implicated in transcription and DNA damage response (Mol Cell 2009, 34: 521-533). Dr. Jha's group has identified the role of TIP60, a histone acetyltransferase in DNA damage response pathway (Mol Cell Biol 2008, 28: 2690-2700) and RVB1, a component of TIP60 complexes to be required for activity of this complex (Mol Cell Biol 2013, 33: 1164-74). Following which, his group has discovered Human Papillomavirus (HPV) E6 and Adenovirus (AdV) oncogenes to destabilize TIP60 (Mol Cell 2010, 38: 700-711; Oncogene 2013, 32: 5017-25 and Oncogene 2016, 35:2062-74). Dr. Jha's have recently identified and new cellular regulator of TIP60 and have demonstrated its role and significance in epithelial-mesenchymal transition and breast cancer progression (Oncotarget 2015, 6:41290-306 and J Mol Cell Biol 2016, 85: 384–399).

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