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Hacking of TIP60.com by human papillomaviruses: How and why?

Sudhakar Jha[1,2], Vanitha Krishna Subbaiah[1], Yanzhou Zhang[1], Deepa Rajagopalan[1, 2], Lissa Nurrul Abdullah[1], Nicole Shu Ling Yeo-Teh[1,3], Tomaic Vjekoslav[4], Lawrence Banks[4], Michael P Myers[4] and **Edward Kai-Hua Chow[1, 2]**

[1]Cancer Science Institute of Singapore, Singapore

[2]Yong Loo Lin School of Medicine, Singapore

[3]National University of Singapore, Singapore

[4]International Centre for Genetic Engineering and Biotechnology, Italy

TIP60 is an essential lysine acetyl transferase, involved in transcriptional regulation, checkpoint activation and p53-directed pro-apoptotic pathways. The cellular levels, stability and activity of TIP60 are tightly regulated. In the case of cervical cancers, we have earlier shown that human papillomavirus (HPV) E6 oncogene of both high and low-risk categories destabilize TIP60. This in turn relieves cellular promoters from TIP60-initiated repression and abrogates p53-dependent activation of apoptotic pathway. Degradation of TIP60, therefore, allows high and low-risk HPV to promote cell proliferation and cell survival. In this conference, I will discuss our efforts to identify the mechanism of TIP60 destabilization by E6 and its implications in cervical cancer progression. Briefly, we have discovered EDD1 (also known as UBR5), an E3 ligase generally overexpressed in cancers as a novel interacting partner of TIP60 and show that EDD1 negatively regulates TIP60's stability through the proteasome pathway. Interestingly, HPV E6 utilizes this function of EDD1 to destabilize TIP60. By using *in vitro* cell culture models and *in vivo* mouse models we show that gain of function of TIP60 or depletion of EDD1 in HPV positive cervical cancer cells significantly inhibits cell growth. In summary, we have discovered a novel ligase through which E6 destabilizes TIP60. Currently, in the absence of an effective therapeutic vaccine, cervical cancer still remains to be a major disease burden. Hence, our studies implying a distinct tumor suppressor role for TIP60 in cervical cancers shows that reactivation of TIP60 could be of therapeutic value.

Biography

Sudhakar Jha is currently working in Yong Loo Lin School of Medicine, Singapore and is a Junior Principal Investigator in Cancer Biology Program, Cancer Science Institute of Singapore. His research focuses on understanding the function of TIP60 (a histone acetyltransferase) as a tumor suppressor. He has discovered TIP60 to be down-regulated by E6, a viral oncogene expressed by human papillomavirus (HPV). Using TIP60 as a candidate molecule, he also plans to investigate how deregulation of this chromatin remodeling complex can lead to cancer.

csisjha@nus.edu.sg

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