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The novel role of tumour suppressor p14ARF in tumour immunology to induce inflammatory response by enhancing SUMOylation

Jennifer Alagu, Yoko Itahana, Bi Xuezhi, Chao Sheng Hao and **Koji Itahana**
National University of Singapore, Singapore

Background: Tumour suppressor p14ARF (alternative reading frame) is activated by oncogenic stress to oncogene-induced senescence *via* activation of p53. The function of ARF is lost in 40% of cancers. Interestingly, loss of ARF has been shown to compound the effect of p53 inactivation highlighting the need to understand the additional functions of ARF. ARF has emerged as a potent up-regulator of global intracellular SUMOylation, independent of p53 activity. However, few targets of ARF-enhanced SUMOylation have been identified and the functional consequences to cancer aetiology remain to be elucidated.

Methods: We employed a novel screening approach combining ARF with SUMO overexpression. Immunoprecipitation of SUMO was performed to identify the proteins SUMOylated in response to ARF by mass spectrometry.

Results: We identified and validated a novel protein target of ARF-enhanced SUMOylation which is a negative regulator of pro-inflammatory transcription factors STAT1 and NF-kB. ARF has been shown to be inducible by IFN-γ and TNF-α, upstream regulators of STAT1 and NF-kB respectively. Our results show that ARF promotes these pro-inflammatory responses by inhibiting this protein by enhancing its SUMOylation status.

Conclusions: Identification of our novel ARF-mediated SUMOylation target reveals ARF's p53-independent role in the pro-inflammatory processes that are activated by tumour invasion or infection of oncogenic viruses to prevent tumourigenesis. Our findings present a novel role of ARF in tumour immunology and given the exceptionally high incidence of ARF loss reported in human cancers, may aid in the development of new therapeutic opportunities for dysregulations observed in the ARF-SUMOylation pathway.

Recent Publications

1. Neo S H (2015) TRIM28 is an E3 ligase for ARF-Mediated NPM1/B23 SUMOylation that represses centrosome amplification. Mol Cell Biol. 35(16):2851-2863.
2. Shoji W (2015) NCYM promotes calpain mediated Myc-nick production in human MYCN-amplified neuroblastoma cells. Biochem. Biophys. Res. Commun. 461(3):501-506.
3. Suenaga Y (2014) NCYM, a Cis-antisense gene of MYCN, encodes a de novo evolved protein that inhibits gsk3β resulting in the stabilization of MYCN in human neuroblastomas. PLoS Genet. 10(1):e1003996.
4. Yamaki T (2013) Temozolomide suppresses MYC *via* activation of TAp63 to inhibit progression of human glioblastoma. Sci Rep. 3:1160.

Biography

Jennifer Alagu obtained her BSc in Biomedical Sciences at Durham University UK in 2011. She then went to work at the Chiba Cancer Center, Japan until 2013 as a Research Assistant where she co-authored 3 publications in the field of Neuroblastoma. Since then, she has been working on her PhD thesis at Duke-NUS Medical School, Singapore in the Laboratory of Tumour Suppression under Prof. Koji Itahana, specifically researching the involvement of major tumour suppresser p14ARF in the regulation of inflammatory responses such as those activated by oncogenic viruses and tumour progression.

jennifer_alagu@u.duke.nus.edu