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KEYNOTE ADDRESS

The Regulation of p53 in Human Cancer

Sir David Lane, FRS

Chief Scientist, A*STAR, p53 laboratory, 8A Biomedical Grove, #06-06 Immunos, Singapore 138648

E-mail: dplane@p53lab.a-star.edu.sg

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Whole genome sequencing of human cancers has confirmed that mutations in the p53 gene are the most common specific genetic events in human cancer. The strength of the database is now such that we can be sure that this is a final answer. What then does p53 mutation do that is so important and how might we exploit this knowledge for the improved diagnosis and treatment of cancer?

The p53 protein is a highly regulated master transcription factor that is induced by stress and in particular by DNA damage. It induces a complex pattern of transcription that activates cellular repair pathways, as well as cell cycle arrest and apoptotic processes all of which act to prevent cancer formation. Mutations in p53 result in loss of these tumor suppressor functions, but some point mutations additionally convert p53 into a driver oncogene. For this gain of function to be realised, the mutant protein must be expressed at high levels.

Using mice homozygous for mutant p53 and mice treated with proteosome inhibitors to stabilize p53, we have carried out an extensive investigation of the regulation of p53 expression in normal and pre-neoplastic mouse tissue. Interestingly, the p53 gene is only transcribed in proliferating cells and the gene is rapidly turned off as cells differentiate and exit the cell cycle. Protein expression levels are very modest and high levels of expression are only reached in tumor cells and in some pre-neoplastic conditions.

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