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Cell transformation by viral oncoproteins - PP2A connection

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Viral proteins capable of altering function of host cell signaling circuits have been shown to participate on the process of transformation of normal human cells to cancer cells. Moreover, viral oncoproteins have been for decades used as research tools to modify activity of their target signaling proteins as well as for elucidating mechanisms involved in human oncogenesis. Protein phosphatase 2A (PP2A) is a human tumor suppressor and its inhibition has been shown to be one of the prerequisites for human cell transformation. These conclusions are mostly based on experimentation in which simian virus 40 (SV40) encoded small-t antigen protein has been expressed in human immortalized cell lines and it has been shown that the capacity of small-t to induce cellular transformation is dependent on its capacity to bind to its cellular target PP2A. In addition to SV40 small-t, also adenoviral E4orf4 and mouse polyoma virus middle-T antigen have been shown to promote malignant transformation by their capacity to inhibit PP2A. Therefore it is expected that further understanding of the role and regulation of PP2A would help us in identifying new mechanisms related to viral oncogenesis.

Even though PP2A inhibition by viral proteins has elucidated important mechanism by which these viral proteins modify cancer cell signal transduction, the mechanisms by which PP2A activity is regulated in human cancers have been poorly understood. In this regard, we have recently identified a novel oncogenic protein CIP2A that inhibits PP2A in human malignancies (Junttila et al., *Cell*, 130, 51–62, 2007). CIP2A prevents c-Myc proteolytic degradation and *in vivo* tumor formation. Importantly, CIP2A is overexpressed in several common human malignancies including head and neck cancers. In addition to CIP2A, our laboratory has recently characterized oncogenic role of another PP2A inhibitor protein PME-1. Our results demonstrate that PME-1-mediated inhibition of the PP2A promotes ERK pathway activity. In malignant gliomas, PME-1 expression levels correlate with cell proliferation and PME-1 expression significantly correlates with disease progression in human astrocytic gliomas (Puustinen et al., *Cancer Research*, *69*, *2870-2877*, *2009*). Together, these observations identify novel mechanisms by which PP2A tumor suppressor activity is inhibited in human malignancies independently of viral proteins.

Biography

Jukka Westermarck (b. 1969) received his M.D. in 1996 and Ph.D in 1998 at the University of Turku. He was a postdoctoral fellow at European Molecular Biology Laboratory in Heidelberg, Germany, in Dr. Dirk Bohmann´s laboratory during 1999-2001. He was a Academy of Finland senior scientist during 2002-2007 and 2006-2009 he was appointed as a Group leader at Institute of Medical Technology (IMT), University of Tampere, Finland. In 2008 he was appointed to Research Professor position at Finnish Cancer Institute. 2009 he was appointed to Research director position at Turku Centre for Biotechnology.