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The tumor supressor INPP4B functions as an oncogenic regulator in a subset of melanomas

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Inositol polyphosphate 4-phosphatase type II (INPP4B) negatively regulates PI3K/Akt signaling and has a tumor suppressive role in some types of cancers. However, we have found that it is up-regulated in a subset of melanomas. Here, we report that INPP4B can function as an oncogenic driver through activation of serum- and glucocorticoid-regulated kinase 3 (SGK3) in melanoma. While INPP4B knockdown inhibited melanoma cell proliferation and retarded melanoma xenograft growth, overexpression of INPP4B enhanced melanoma cell and melanocyte proliferation and triggered anchorage-independent growth of melanocytes. Noticeably, INPP4B-mediated melanoma cell proliferation was not related to activation of Akt, but was mediated by SGK3. Up-regulation of INPP4B in melanoma cells was associated with loss of miRNA (miR)-494 and/or miR-599 due to gene copy number reduction. Indeed, overexpression of miR-494 or miR-599 down-regulated INPP4B, reduced SGK3 activation, and inhibited melanoma cell proliferation, whereas introduction of anti-miR-494 or anti-miR-599 up-regulated INPP4B, enhanced SGK3 activation, and promoted melanoma cell proliferation. Collectively, these results identified up-regulation of INPP4B as an oncogenic mechanism through activation of SGK3 in a subset of melanomas, with implications for targeting INPP4B and restoring miR-494 and miR-599 as novel approaches in the treatment of melanomas with high INPP4B expression.

Biography

Xu Dong Zhang has received his PhD degree from the University of Sydney in 2001 and since has been working on translational melanoma research. His major research interest is in regulation of programmed cell death and survival signal pathways in melanoma cells. He is a Professor and Co-Director of the Priority Research Center for Cancer of the University of Newcastle, Australia. He is also the Deputy Director of the Cancer Research Program of the Hunter Medical Research Institute. He has published more than 130 papers in reputed journals with a current H index of 36.

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