Title: The significance of CDK5 activity in melanocyte lineage-specific pathways and melanoma progression

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Abstract

Melanoma is the most lethal form of skin cancer responsible for over 80% of skin-cancer related death. Current reports suggest that melanoma incidence rates rapidly increased in United States and Korea as well. It has been suggested that UV radiation in childhood is a strong risk factor of melanoma development in particular association with melanin pigmentation pathways. Recently approved Vemurafenib, a therapeutic agent for melanoma bearing active oncogenic mutant $Braf^{V600E}$ were shown excellent initial responses in clinic, but the effect of the therapy was only transient in most of treated patients. Therefore, to achieve a durable remission with these agents, it is essential that we find novel therapeutic targets, enhancing B-Raf^{V600E} drug sensitivity and prohibiting the acquisition of therapy resistance.

Since melanocytes are originated from neural crest, we peculated that cyclin-dependent kinase 5 (CDK5), a neuronal kinase may have a conserved role in melnacyte/melanoma development. The increased CDK5 expression was associated with poor survival among metastatic melanoma patients. In our laboratory, the potential role of CDK5 was examined by CDK5 knockdown in human melanoma cell lines which resulted in decreased cell proliferation with novel links with NGF or TGF-β-mediated cellular responses. The pharmacological inhibition or ablation of Cdk5 gene in melanoma mouse model ($Braf^{v600e}$/$Pten^{null}$) showed a significant reduction of tumor development and metastasis to draining lymph nodes. Interestingly, we have a serendipitous finding that active CDK5 restored the pigmentation in melanoma cell line which does not express pigments at normal culture condition. The CRISPR/CAS9-mediated knockout of Cdk5 in B16/F10 melanoma showed a compromised response to α-MSH which resulted in decreased CREB activation, a key transcription factor of Mitf, indicating promising role of CDK5 in Mitf-mediated gene expression.

Very recently, the MITF-dependent melanocyte-lineage specific pathway that regulates cell differentiation, proliferation and pigmentation was depicted as a critical pathway for development of vemurafenib-resistance. In line of this prospect, we are now exploiting the role of Cdk5 in UVR-induced pigmentation and acquiring therapy-resistance of Brafv600e melanoma in mouse melanoma model. Combining together, we propose that co-targeting active CDK5 would enhance B-Raf^{V600E} drug-response through the regulation of melanocyte lineage-specific pathway.