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CDK6-MEDIATED SUPPRESSION OF CD25 IS REQUIRED FOR SELF-RENEWAL OF LSCS

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Despite recent advances in chemotherapy, relapse is frequent, possibly because the available therapies do not eradicate the cells that initiate and sustain the disease *in vivo*, so-called leukemia stem cells (LSCs). Cyclin-dependent kinase 6 (CDK6) regulates cell cycle progression and modulates differentiation of certain cells. It is predominantly expressed in hematopoietic cells and over-expressed in human T-ALL/LBL. To clarify the role of CDK6 in cell cycle control and tumorigenesis, I have generated mice with targeted mutations in Cdk6. These "knock-in" alleles generate hyperactive or inactive kinase subunits that may better mimic hyperactivation of CDK6 in tumor cells or model pharmaceutical inhibition of CDK6, respectively. We have found that CDK6 is required for initiation and maintenance of T-ALL leukemia and lymphomagenesis induced by constitutively active Notch/Myr-AKT. Pharmacologic inhibition of CDK6 kinase induces CD25 expression, cell cycle arrest, and apoptosis in mouse and human T-ALL. Ablation of Cd25 in a K43M background restores Notch-induced T-leukemogenesis, with disease that is resistant to CDK6 inhibitors *in vivo*. Moreover, loss of Cd25 in a K43M background restore the ability of LSCs to self-renew. These data support a model whereby CDK6-mediated suppression of CD25 is required for initiation of T-ALL by activated Notch1, and CD25 induction mediates the therapeutic response to CDK6 inhibition in established T-ALL. These results both validate CDK6 as a molecular target for therapy of this subset of T-ALL and suggest that CD25 expression could serve as a biomarker for responsiveness of T-ALL to CDK4/6 inhibitor therapy.

Figure. A working model of the role of CDK6 in T-ALL. In response to stimuli, increased expression of cyclin D1 and CDK6 leads to increased CDK6 activation, while Notch1 and AKT1 are also independently activated in parallel. Notch1 further activates CDK6 via upregulation of CDK6 and/or by increased cyclin D3 protein, while AKT1 activates CDK6 through the stabilization of cyclin D2. Once activated, CDK6 can phosphorylate pRB, resulting in its inactivation. CDK6, along with ERK and CDK1 can also phosphorylate RUNX1 thereby promoting RUNX1 proteolytic degradation. On a different molecular path, phosphorylation of FOXM1 by CDK6 stabilizes FOXM1, which in turn promotes methylation of the GATA3 promoter, decreasing GATA3 expression and the subsequent recruitment to the CD25 proximal promoter region. CD25 expression is consequently reduced and T-ALL develops. Devoid of CDK6 protein/kinase activity, pRB and RUNX1 remain active, which suppress the tumorigenesis in CD25-independent manner. Contrastingly, without CDK6, FOXM1 is in its inactive state, leading to CD25 upregulation. Overall, T-ALL is suppressed by FOXM1 inactivity, and by increasing RUNX1, pRB, GATA3, and CD25 expression or activity.

BIOGRAPHY

Miaofen G Hu has completed her PhD from Boston University School of Medicine and post-doctoral studies from Harvard University School of Medicine. She has been Assistant Professor at TUFTS medical Center since 2011. She has published 24 papers in reputed journals. Her most significant research accomplishments thus far include creating a CDK6 mouse model, discovering the role of CDK6 as a common mediator of Notch1 and AKT1 signaling pathways, establishing the potential therapeutic role of CDK6 in T cell malignance, revealing the function of CDK6 kinase activity in negatively regulating the conversion of fat-storing cells into fat-burning cells.

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