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Role of WW domain-containing oxidoreductase WWOX in driving T-cell acute lymphoblastic leukemia maturation

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Whether tumor suppressor WWOX stimulates immune cell maturation is largely unknown. Here, we determined that Tyr33-phosphorylated WWOX physically binds non-phosphorylated ERK and IκBα in immature acute lymphoblastic leukemia MOLT-4 T cell and in the naïve mouse spleen. The IκBα/ERK/WWOX complex was shown to localize, in part, in the mitochondria. WWOX prevents IκBα from proteosomal degradation. Upon stimulating MOLT-4 with ionophore A23187/phorbol myristate acetate (IoP), endogenous IκBα and ERK undergo rapid phosphorylation in less than 5 min, and subsequently WWOX is Tyr33 and Tyr287 de-phosphorylated and Ser14 phosphorylated. Three hr later, IκBα starts to degrade and ERK returns to basal or non-phosphorylation, and this lasts in the next 12 hr. Finally, expression of CD3 and CD8 occurs in MOLT-4, along with re-appearance of the IκBα/ERK/WWOX complex near 24 hr. Inhibition of ERK phosphorylation by U0126 or IκBα degradation by MG132 prevents MOLT-4 maturation. By time-lapse FRET microscopy, IκBα/ERK/WWOX complex exhibits an increased binding strength by 1-2 fold after exposure to IoP for 15-24 hrs. Meanwhile, a portion of ERK and WWOX relocate to the nucleus, suggesting their role in the induction of CD3 and CD8 expression in MOLT-4. (Supported by MOST and NHRI, Taiwan, and DoD, USA)

Biography

Nan-Shan Chang is currently the Professor and Director of the Molecular Medicine Institute, National Cheng Kung University (NCKU) in Taiwan, and the Adjunct Professor with the SUNY Upstate Medical University and the NYS Institute for Basic Research in Developmental Disabilities, New York. Dr. Chang is most noted for his discovery of tumor suppressor WWOX in 2000. Recent Awards: Breast cancer and neurofibromatosis research awards from the Department of Defense, USA, in 2008 and 2010; NCKU Distinguished Professor Award 2010, 2013 and 2016; Distinguished Scientist Award 2011 from the Society of Experimental Biology & Medicine, USA.

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