



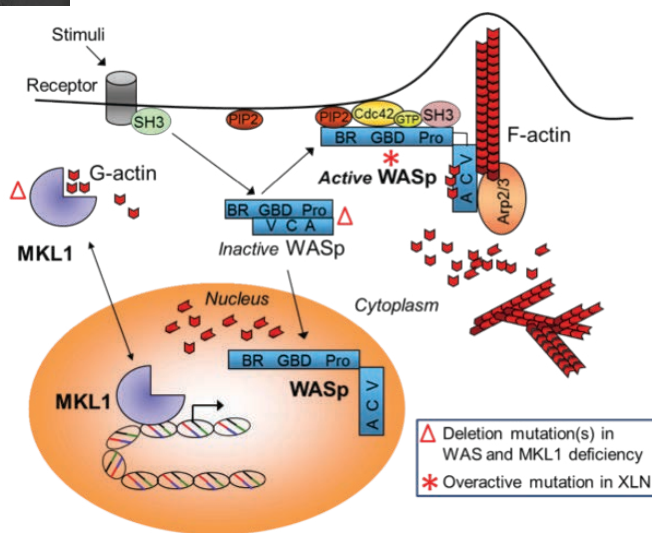
ICGEB International SEMINAR PROGRAMME 2018

Tuesday, 27 March 2018 | 3:00 pm | ICGEB Seminar Room, W building | Padriciano, 99, Trieste, ITALY



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The actin cytoskeleton is essential for life and regulates critical processes such as cell division, cell migration and cell-to-cell communication. The Wiskott-Aldrich syndrome protein (WASp) family induces actin polymerisation from existing actin filaments via the Arp2/3 complex to form a dynamic actin network. Megakaryoblastic Leukaemia 1 (MKL1) regulates G-actin concentration in the cytoplasm. The importance of correct regulation of the actin cytoskeleton dynamics is revealed in rare and severe primary immunodeficiency diseases with high incidence of tumours and autoimmunity. Wiskott-Aldrich syndrome (WAS) is caused by loss-of-function mutations in WASp and patients suffer from life-threatening infections and bleedings. In contrast to WAS, X-linked neutropenia (XLN) is caused by gain-of-function mutations predicted to lead to a constitutively-active WASp. XLN patients suffer from severe congenital neutropenia and are at risk to develop malignancies. MKL1 deficiency was recently identified in a child with severe recurrent major infections. Moreover, two out of three male triplets with an intragenic deletion of MKL1 developed Hodgkin lymphoma in adulthood. We have used new animal models and rare patient samples to address how neutrophils and B cells are affected in patients with mutations in WASp and MKL1. We found that there are unique requirements for the presence and activation status of WASp in neutrophils and that activating mutations in WASp render neutrophils hyperactive. Moreover, we found that the intragenic deletion of MKL1 in triplets with Hodgkin lymphoma leads to increased MKL1 expression and abnormal B cell responses and genomic instability. Together, this data suggests that the activity of WASp and MKL1 needs to be fine-tuned for correct activity of neutrophils and B cells.

“The immune system is never at rest: Understanding the role of actin regulators in immune cells”

Host: F. Benvenuti

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