Life Sciences Seminar

WASp mediated Arp2/3 activation controls endo-lysosomal fusion and cargo degradation determining the threshold for Toll-like receptor 9 activation

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Dendritic cells are central to initiate responses to viruses and transformed cells. In the lab we focus on pathological contexts where DCs functions are deviated from normal, trying to understand the underlying cell biological mechanism.In DCs derived from a mouse model of Wiskott-Aldrich syndrome, a rare primary immune deficiency, lack of the actin nucleation-promoting factor WASp causes defects in cell migration and interaction with T cells. In addition to this established cellular defects, we discovered that signalling from endosomal Toll-like receptor 9 is enhanced in WASp null cells, leading to excessive production of type-I interferon and chronic inflammation. We investigated the basis of excessive signalling by tracking the intracellular journey of TLR9 ligands and the overall morphology and function of the endocytic system. We found that WASp controls endo-lysosomal fusion and delivery of endocytic cargo to lysosomes for degradation. Lack of WASp, or chemical inhibition of Arp2/3, causes accumulation of cargo and receptor and lowers the threshold for receptor activation. These findings help to explain the enhanced sensitivity to low amount of innate triggers and the susceptibility to develop autoimmune phenomena in Wiskott-Aldrich syndrome. A second interest of the lab is to understand the mechanisms of DC suppression in lung tumors. We have found that lung tissue resident type-1 DCs, specialized in cross-presentation of antigens, loose the capacity to activate CD8+ T cells in tumors. Transcriptomic analysis of lung tumor-associated DC1 showed changes in pathways of antigen uptake and intracellular trafficking. Loss of a specific phosphatydilserine receptor suggests that cancer cell may escape immune recognition by targeting uptake and acquisition of tumor antigens by DC1, an essential step in priming of anti-tumor T cell responses.

Friday, April 6, 2018 10:00am - 11:00am
Mondi Seminar Room 2, Central Building

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