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Title: **Critical functional and morphological role of Arp2/3 in T lymphocytes**

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**Abstract (600 word limits)**

Cytotoxic effector T lymphocytes (CTL) provide immunosurveillance against invading pathogens and malignant cells and utilize amoeboid migration to navigate effectively within complex microenvironments. Efficient migration and function rely on the precise rearrangement of the actin cytoskeleton. This extensive remodelling is mediated by actin nucleators such as the Arp2/3 complex, a macromolecular machine that nucleates branched actin filaments at the leading edge. T cells are assumed to exclusively utilize lamellipodia- or filopodia-based locomotion, even when migrating using an integrin-independent strategy. However, the consequences of modulating Arp2/3 activity on the biophysical properties of the actomyosin cortex and downstream T cell function are incompletely understood. To explore the consequences of modulated Arp3 expression levels in CTL, we employed a retroviral knockdown strategy to generate Arp3 knockdown CTL from naïve T cells isolated from OT-I TCR transgenic mice. We report that even a moderate decrease of Arp3 levels in T cells profoundly affects actin cortex integrity. Reduction in total F-actin content leads to reduced cortical tension and disrupted lamellipodia formation. Instead, Arp3-knockdown cells switch to a blebbing migration mode characterized by transient, balloon-like protrusions at the leading edge. Although blebbing migration is compatible with interstitial migration in three-dimensional environments, diminished locomotion kinetics and impaired cytotoxicity interfere with optimal T cell function. These findings define that the Arp2/3 complex's role is not redundant among the various mechanochemical coordinators involved in the leading-edge formation in CTL and the membrane integrity in CTL activities is Arp2/3-dependent.

**Biography (200 word limit)**

Peyman Obeidy`s fundamental research interest is the integration of cancer biology, immunology and biophysics. During his postdoctoral work at Professor Wolfgang Weninger's laboratory, he manipulated the expression of Arp2/3, one of the critical actin nucleators, by the shRNA-mediated knockdown. Findings from this study expand our knowledge of the regulation of the actomyosin cortex in T cells. His PhD study was focused on dissecting the molecular mechanisms that underpin the functional specialization of the actin cytoskeleton. Using fluorescence imaging and single-

molecule analysis, he developed microfluidics assays and succeed in detecting the binding of single tropomyosins into polymers with actin in vitro. In the biomedical field, he worked on the development of applications and assays which pave the way for more accurate and accessible therapies.

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