Universität Basel

Research Project

Investigating the role for coronin 1 in T cell homeostasis and immune tolerance

Third-party funded project

Project title Investigating the role for coronin 1 in T cell homeostasis and immune tolerance
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Cells within tissues and organs need to maintain homeostatic numbers to function properly. While in many tissues this is achieved through heterotypic cell-to-cell interaction and/or the sensing of growth factor gradients, for individually circulating cells such as T cells, that are known to populate their space at near-constant numbers, it is unknown what determines their exact population size. In addition, dysregulation of T cell homeostasis is associated with autoimmune diseases, pathological reactions against transplanted organs, and cancers.Whereas thus far, T cell homeostasis has been attributed to T cell receptor (TCR) signaling through Major Histocompatibility Complex (MHC)-self peptides and/or interleukin-7 (IL-7) signaling, recent work from our laboratory suggests the existence of a third pathway that is independent of TCR/interleukin-7, and is instead regulated by coronin 1. Coronin 1 is a member of the evolutionary conserved Tryptophan-Aspartate (WD) repeat protein family of coronins, that are widely expressed in all eukaryotic organisms. Although the molecular function of coronin molecules has been linked to a role in F-actin rearrangement, more recent work suggests that coronin 1 regulates T cell homeostasis in an F-actin-independent manner, but the mechanisms via which coronin 1 does so remain unknown. In the previous granting period we have uncovered a role for coronin 1 in the regulation of cyclic Adenosine Mono Phosphate (cAMP)-dependent signal transduction in T cells. Notably, we found that coronin 1 deletion results in the establishment of a cAMP-dependent immunosuppressive environment thereby dampening auto- and alloimmune responses. Importantly, we found that disruption of coronin 1 signaling in T cells promotes allograft tolerance while maintaining anti-pathogen immunity. In work that is currently being prepared for submission, we show that this pathway can be targeted to prevent autoimmunity, and we therefore believe that we have been able to significantly contribute novel insight towards an important problem. In the next granting period, we aim to address 2 main aims. First, we aim to delineate the molecular mechanism underlying coronin 1-dependent T cell homeostasis, through (i) analyzing the signal transduction cascade(s) in which coronin 1 is involved; (ii) defining the coronin 1 interactome in T cells and (iii) unraveling the regulatory network involved in coronin 1 transcription. Second, we aim to understand the induction of selective immunosuppression induced by coronin 1 deletion. This will be achieved by analyzing the mechanism of immunosuppression upon coronin 1 deletion as well as dissect the molecular pathways involved in allo- and auto-immune responses versus anti-pathogen responses. These aims will be addressed using a combination of state-of-the-art biochemical, molecular and cell biological techniques, including siRNA- and CRISPR/Cas9-based screening, total transcriptome analysis and mass spectrometry as well as stem cell-based reconstitution of T cell homeostasis in animal models. We believe that this work will allow to define a hitherto unknown signal transduction pathway regulating T cell homeostasis as well as contribute to the further characterization of an entirely novel and targetable pathway selectively involved in allo-and autoimmune responses. Finally,

given the observed parallels between the role for coronin 1 in T cell homeostasis and coronin A's role in the regulation of growth and multicellular development in the lower eukaryote Dictyostelium discoideum, the work proposed here may allow to unravel a hitherto uncharacterized signaling pathway involved in cellular homeostasis conserved from amoeba to humans.

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