Spred1 Safeguards Hematopoietic Homeostasis against Diet-Induced Systemic Stress.

Journal: Cell Stem Cell

Publication Year: 2018

Authors: Yuko Tadokoro, Takayuki Hoshii, Satoshi Yamazaki, Koji Eto, Hideo Ema, Masahiko Kobayashi, Masaya Ueno, Kumiko Ohta, Yuriko Arai, Eiji Hara, Kenichi Harada, Masanobu Oshima, Hiroko Oshima, Fumio Arai, Akihiko Yoshimura, Hiromitsu Nakauchi, Atsushi Hirao

PubMed link: 29706577

Funding Grants: Generation of functional cells and organs from iPSCs

Public Summary:
Our diet and microbiome have a big influence on our bodies, but how these directly influence tissue stem cell function remains poorly understood. In this paper, we investigated how molecular pathways involved in blood stem cell maintenance were influenced by a high-fat diet. We identified a gene called Spred1 as playing an important role in stem cell activity and as a tumor suppressor in the context of a high-fat diet. These findings are helping us to understand the links between metabolism and stem cell activity.

Scientific Abstract:
Stem cell self-renewal is critical for tissue homeostasis, and its dysregulation can lead to organ failure or tumorigenesis. While obesity can induce varied abnormalities in bone marrow components, it is unclear how diet might affect hematopoietic stem cell (HSC) self-renewal. Here, we show that Spred1, a negative regulator of RAS-MAPK signaling, safeguards HSC homeostasis in animals fed a high-fat diet (HFD). Under steady-state conditions, Spred1 negatively regulates HSC self-renewal and fitness, in part through Rho kinase activity. Spred1 deficiency mitigates HSC failure induced by infection mimetics and prolongs HSC lifespan, but it does not initiate leukemogenesis due to compensatory upregulation of Spred2. In contrast, HFD induces ERK hyperactivation and aberrant self-renewal in Spred1-deficient HSCs, resulting in functional HSC failure, severe anemia, and myeloproliferative neoplasm-like disease. HFD-induced hematopoietic abnormalities are mediated partly through alterations to the gut microbiota. Together, these findings reveal that diet-induced stress disrupts fine-tuning of Spred1-mediated signals to govern HSC homeostasis.

Source URL: https://www.cirm.ca.gov/about-cirm/publications/spred1-safeguards-hematopoietic-homeostasis-against-diet-induced-systemic