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Geminin regulates self-renewal and cell fate decisions in haemopoietic stem cells

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Abstract

Stem and progenitor cells are able to self-renew or initiate a fate determination program that generates committed progenitor cells with limited self-renewing ability, which then activate functionally specialised programs and give rise to differentiated cells. Stem and progenitor cells are integrating signals from their microenvironment and coordinate intracellular signalling that includes transcriptional networks, chromatin organisation and cell cycle progression in order to regulate these processes and meet the physiological needs of the organism.

Multiprotein complexes affecting chromatin remodelling and epigenetic marks, in concerted action with key transcription factors, have been suggested to regulate self-renewal and commitment decisions. Recent studies suggest that the cell cycle inhibitor Geminin might be involved in controlling these processes. Balanced interactions of Geminin with Cdt1, transcription factors, SWI/SNF and Polycomb complexes are believed to balance proliferation and differentiation decisions. We have shown, using conditional knockout mice for Geminin, that Geminin is not required in vivo for the maintenance of genomic integrity in all cell types, while it plays an important role during T cell activation. Conditional inactivation and overexpression experiments point to an essential role for Geminin for the maintenance of a balance between self-renewing progenitor cells and differentiating cells in the developing and adult cortex.

Moreover, we show that inactivation of Geminin in haematopoietic stem cells (HSCs) results in early embryonic lethality with embryos exhibiting reduced fetal liver cellularity. The haematopoietic stem cell compartment and committed progenitors and differentiated cells is severely affected. Transcriptomics analysis and chromatin immunoprecipitation experiments revealed a gene network regulated by Geminin both at the transcriptional and epigenetic level, suggesting a key role for Geminin in the regulation of self-renewal and fate commitment decisions in HSCs and neural stem cells.

Biography

Stavros Taraviras is Associate Professor at the Department of Physiology at the Medical School, University of Patras, Greece. He holds a Ph.D from the University of Heidelberg, Germany and performed postdoctoral research appointments at the German Cancer Research Center in Heidelberg and the MRC/National Institute for Medical Research in London, UK. He is a reviewer for national and international funding agencies and scientific journals. He has published more than 35 papers in high profile journals. He serves as an editorial board member for the European Journal of Molecular Biology, Frontiers in Biosciences, International Journal of Pharmacy and Biomedical Sciences and Stem Cell Discovery.