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Transcriptional Quiescence of Physiological and Cancer Stem Cells

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Adult stem cells have the exceptional ability to undergo continuous self-renewal and differentiation, which is essential for tissue homeostasis and response to injury. These cells are resistant to most cytotoxic stresses but retain the capacity for rapid activation upon stimulation. While cellular quiescence is thought to be the key mechanism underlying these essential features of the stem cell system, the molecular basis of induction and maintenance of quiescence is unresolved. Previous data from our lab has demonstrated that adult melanocyte stem cells (MelSC) down regulate housekeeping gene expression, suggesting a global suppression of mRNA transcription. We then showed, using antibodies against specific phosphorylated forms of RNA polymerase II (RNApII), that adult MelSC are negative for productive mRNA transcription elongation, while RNApII is activated and initiated, ready to synthesize mRNA upon appropriate stimulation. In line with this, the RNApII kinase CDK9 was absent in adult MelSC. Inhibition of CDK9 resulted in improved survival of cells deprived of growth factors, and induced a stem cell like phenotype in primary embryonic melanoblasts. Interestingly, also other adult stem cells, including keratinocyte, muscle, spermatogonia and haematopoietic stem cells, showed a similar absence of RNApII phosphorylation.

We conclude that absence of productive mRNA transcription is an early, specific and conserved feature of adult stem cells. Down regulation of mRNA transcription might lead to decreased rates of metabolism and protection from cellular and genetic damage. Screening heterogeneous tissues, including cancer, for transcriptionally quiescent cells, might result in the identification of cells with a stem cell like phenotype.

Biography

After obtaining his Master Degree in Pharmacology from University of Leipzig, Germany, R.Freter completed his Ph.D. in Shin-Ichi Nishikawa's Laboratory for Stem Cell Biology at the RIKEN Center for Developmental Biology, Kobe, Japan. Currently, he is a postdoctoral researcher in Colin Goding's laboratory at the Ludwig Institute for Cancer Research, University of Oxford, UK. His work focuses on transcriptional quiescence as a marker for physiological and cancer stem cells. Using cell lines, mouse models and primary human samples he works towards a better understanding of melanoma relapse and metastasis.