Cell cycle function in stem cell differentiation.

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Understanding the mechanisms controlling cell fate decisions in stem cells is of great interest since regulation of differentiation is necessary for embryonic development, organ homeostasis and tissue repair. Consequently, a considerable knowledge has been accumulated concerning the function of signalling pathways, transcription factors and epigenetic modifiers in controlling differentiation. Nonetheless, a broad number of studies have characterised the differences between stem cells and their differentiated progenies while the dynamic mechanisms occurring during the process leading to differentiation remains more elusive. More precisely, most mammalian stem cells differentiate while undergoing cell division to produce daughter cell(s) with a different identity. However, the importance and potential function of cell cycle progression in differentiation has not yet been fully uncovered.

Human pluripotent stem cells (hPSCs) induced (hIPSCs) or embryonic (hESCs) have an unsurpassed interest to study these mechanisms. Indeed, they can proliferate indefinitely in vitro while maintaining the capacity to differentiate into a homogenous population of endoderm, mesoderm and neuroectoderm cells. This process follows a natural path of development and has already been useful to discover mechanisms relevant for the formation of these germ layers *in vivo*. hPSCs are also compatible with genome wide analyses while a diversity of tools is now available to study gene function during their differentiation.

Here, I will describe data showing that hPSCs undergo symmetric divisions during their differentiation. Each cell division is associated with the production of new cell type. Furthermore, this cell cycle progression is associated with precise change in epigenetic marks which leads to the acquisition of a new cellular identity. However, cell division appears to be necessary only for cell fate commitment and not for cell fate specification. On the other hand, cell cycle regulators are necessary for the expression of key differentiation markers indicating that that the cell cycle machinery could coordinate directly the molecular mechanisms orchestrating differentiation. Taken together, these results demonstrate that precise molecular interplays coordinate cell cycle progression and differentiation in stem cells