Differentiation of murine embryonic stem cells (mESCs) and murine induced pluripotent stem cells (miPSCs) into Clara cells via enhanced definitive endoderm formation

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Published on 23 Oct 2010

Clara cells are non-mucous and non-ciliated secretory cells of the conducting airways. One of their major function is to protect the bronchiolar epithelium of mammals and the upper airways of some species such as mice by producing several products like the Clara cell secretory protein (CCSP). Furthermore, they may serve as progenitor/stem cells. Currently, allogeneic lung transplantation seems to be the only alternative to treat patients with terminal pulmonary failure. However, the limiting factor is the shortage of donor organs. Therefore, the ability to produce Clara cells in vitro would offer new therapeutic options to treat pulmonary injuries and diseases, including genetic disorders like cystic fibrosis. Pluripotent stem cells might be a suitable source to produce Clara cells in vitro. In contrast to ESCs the new technique of producing iPSCs offers perspective to produce patient-specific Clara cells in the future. The aim of this work is to increase the yield of Clara cells derived from mESCs and miPSCs via enhanced definitive endoderm formation.

In this context, we are testing the influence of different substrates and growth factors on the monolayer-based differentiation. To determine the percentage of mesendoderm and definitive endoderm in the early differentiation cultures, we are using a transgenic mESC line, kindly provided by the group of G. Keller, that expresses eGFP from the brachyury locus and a truncated version of the human CD4 from the foxa2 locus. Moreover, in collaboration with M. Mall of the University of Heidelberg, a transgenic mice was established that expresses eGFP and lacZ from the CCSP locus. A miPSC clone from these transgenic mice was established and successfully differentiated into lacZ positive Clara cells.