Differentiation of pluripotent stem cells into retinal pigmented epithelium.

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Authors: Roxanne H Croze, Dennis O Clegg

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Public Summary:
Nuclear factor, erythroid 2□like 2 (Nrf2) is a master transcription factor for cellular defense against endogenous and exogenous stresses by regulating expression of many antioxidant and detoxification genes. Here, we show that Nrf2 acts as a key pluripotency gene and a regulator of proteasome activity in human embryonic stem cells (hESCs). Nrf2 expression is highly enriched in hESCs and dramatically decreases upon differentiation. Nrf2 inhibition impairs both the self□renewal ability of hESCs and reestablish□ ment of pluripotency during cellular reprogramming. Nrf2 activation can delay differentiation. During early hESC differentiation, Nrf2 closely co□ localizes with OCT4 and NANOG. As an underlying mechanism, our data show that Nrf2 regulates proteasome activity in hESCs partially through proteasome maturation protein (POMP), a proteasome chaperone, which in turn controls the proliferation of self□renewing hESCs, three germ layer differentiation and cellular reprogramming. Even modest proteasome inhi□ bition skews the balance of early differentiation toward mesendoderm at the expense of an ectodermal fate by decreasing the protein level of cyclin D1 and delaying the degradation of OCT4 and NANOG proteins. Taken to□ gether, our findings suggest a new potential link between environmental stress and stemness with Nrf2 and the proteasom

Scientific Abstract:
Ocular diseases affect millions worldwide and dramatically influence the quality of life. Although much is known about ocular biology and disease pathologies, effective treatments are still lacking. The eye is well suited for application of emerging cell-based therapies. This chapter explores the development of stem cell-based treatments for age-related macular degeneration (AMD), a prevalent ocular disease in the elderly. Retinal pigmented epithelium (RPE), a cell type implicated in AMD, has been derived from both induced pluripotent stem cells and embryonic stem cells (ESC). Rapidly advancing research has generated various methods of RPE differentiation and several transplantation strategies. Clinical trials are already underway using suspensions of ESC-derived RPE and others are soon to follow. This chapter will provide an overview of current derivation and transplantation strategies for stem cell-derived RPE for the treatment of AMD and other related ocular diseases.