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Epithelial-mesenchymal transition in colonies of rhesus monkey embryonic stem cells: a model for processes involved in gastrulation?

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The ability to give rise to differentiated cell types that are derived from all three primary germ layers of the embryo is what makes embryonic stem (ES) cells unique. However, our understanding of the developmental potential of ES cells is still fragmentary. Rhesus monkey ES cells were grown on mouse embryonic fibroblast (MEF) feeder layers for up to ten days to form multilayered colonies. Within this period, stem cell colonies differentiated spontanously into complex structures with a disc-like morphology. These colonies were characterised by morphology, immunohistochemistry and marker mRNA expression (ISH, RT-PCR) in order to identify processes of epithelialisation as well as epithelial-mesenchymal transition (EMT). Typically, differentiated colonies were composed of an upper and a lower layer, the former growing on top of the layer of MEF feeder cells whereas the lower rhES cell layer spread out underneath the MEF feeder cells. Cells in the upper layer formed an epithelium whereas cells in the lower layer expressed a mesenchymal phenotype. Interestingly, in the central part of the colonies, a roundish pit developed and upper layer rhES cells seemed to ingress here through a defect in the MEF feeder layer to form the lower ES cell layer while undergoing a transition from an epithelial to a mesenchymal phenotype. This switch of phenotype was indicated by a loss of the protein ZO-1, which is a marker for epithelial cells. Phenotypic changes of this type are known as a characteristic of the EMT that takes place at vertebrate gastrulation. Accordingly we found a 10-fold up-regulation of the gene *snail2*, which is a key regulator of the process of EMT and suppresses the epithelial phenotype. Conversion of epiblast to mesoderm was also suggested by the regulated expression of the mesoderm marker *brachyury* during colony differentiation. Thus, these rhES cell colonies may be an interesting model for studies on some basic processes involved in early primate embryogenesis.

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