

Modifying the Fate of Human Embryonic Stem Cells

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Human embryonic stem (ES) cells hold considerable promise for deciphering the processes of human embryonic development, elucidating the mechanisms of oncogenesis, and providing a source of differentiated, functional cells for use in regenerative medicine. The key to each of these opportunities lies in understanding the molecular mechanisms that regulate the fate of ES cells, the decisions made by between self renewal and commitment to differentiation.

Embryonal carcinoma (EC) cells from teratocarcinomas offer a paradigm for the study of ES cells, and have contributed to the development of many tools and concepts that are applicable to ES cells. Moreover, as malignant counterparts of ES, EC cells may provide insights into how ES cells adapt after long periods in culture. Both cells are immortal and capable of indefinite proliferation, but can also differentiate into cells with a limited proliferative capacity. Upon prolonged culture human ES cells may acquire features typical of EC cells, including the capacity to form tumors that continue to retain undifferentiated stem cells. For EC cells in tumors and ES cells in culture there is likely to be a common selective pressure for genetic changes that alter the balance between self-renewal and differentiation. Our own results highlight genetic and epigenetic changes that occur both in human ES cells on prolonged passage, and in EC cells in tumors. Specifically, we have found that frequent amplification of chromosomes 17, 12 and X occurs in human ES cells upon prolonged culture, and similar amplifications are also typical of human EC cells from teratocarcinomas. It seems likely that amplification of particular genes located on these chromosomes are responsible for an enhanced growth potential that would accompany genetic changes that promote self renewal at the expense of differentiation or apoptosis. Identification and understanding the nature of these genes may provide insights into the mechanisms that control the behavior of ES cells in culture, and their eventual fate. It may also give insights into cancer progression since genetic changes

that favor self renewal over differentiation are likely to lead to the appearance of more aggressive cancers. Our current studies, both of genes located on these chromosomes, and of genes differentially expressed between early and late passage human ES cells, have identified a number of candidates that may play a role in maintaining the undifferentiated state of human ES cells.