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Authors

Roy, Somdutta
Gascard, Philippe
Dumont, Nancy
[et al.](#)

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Abstract LB-273: The tumor suppressor p16^{INK4a} regulates extensive plasticity in rare somatic cells found in adult human tissue.

Somdutta Roy; Philippe Gascard; Nancy Dumont; Jianxin Zhao; Deng Pan; Sarah Petrie; Marta Margeta; Thea Dorothy Tlsty

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Abstract

Extensive studies have demonstrated that repression of p16^{INK4a} (CDKN2A) not only silences a powerful tumor suppressor activity, but also is associated with the acquisition of a plastic state, i.e. the ability of a cell to change phenotypes. In epithelial cells, repression of p16^{INK4a} does not only inactivate cell cycle arrest in response to stress but also allows increased expression of chromatin remodeling proteins that are important for epigenetic plasticity underlying differentiation. The up-regulation of such chromatin remodeling proteins sets the expression pattern of pluripotent cells in *Drosophila* and inhibits differentiation and dictates the decision between progenitor and differentiated states in murine myoblasts. Furthermore, mice engineered for knock-out of BMI-1, a polycomb protein that inhibits p16^{INK4a} transcription, fail to repress p16^{INK4a} activity and fail to generate hematopoietic and neural stem cells. In light of these observations, we reasoned that repression of p16^{INK4a} might also modulate expression of cell surface markers that could be used for the prospective isolation of stem or progenitor cells.

We identified cell surface markers associated with repression of p16^{INK4a} and found that they allowed direct isolation of rare cells from healthy human breast tissue that exhibit extensive lineage plasticity. This subpopulation of cells has the ability to transcribe pluripotency markers, Oct3/4, Sox2 and Nanog at levels similar to those measured in human embryonic stem cells and to acquire a plastic state sensitive to environmental programming. *In vitro*, *in vivo* and teratoma assays demonstrated that either a directly-sorted (uncultured) or a single cell (clonogenic) cell population from primary human tissue can differentiate into functional derivatives of each germ layer, ectodermal, endodermal and mesodermal. In contrast to other cells that express Oct3/4, Sox2 and Nanog, these human endogenous Plastic Somatic cells (ePS cells) are mortal, express low telomerase activity, expand for an extensive but finite number of population doublings, and maintain a diploid karyotype before arresting in G1. The observation that repressed p16^{INK4a}, a key tumor suppressor gene, is associated with epigenetic and phenotypic plasticity suggests functional links between tumor suppressor genes and plastic states that are yet to be determined and may some day be exploited for cancer intervention.

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