Human Stem Cell Proliferation and Differentiation: Lessens From a Lost Era of Research

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In the last decade with the advent of methodologies to culture human embryonic stem cells (hESC) and to generate induced pluripotent stem (iPS) cells from terminally differentiated tissues, there has been an enormous surge in research aimed at differentiating human stem cells into a plethora of different tissue types for use in regenerative medicine. Regenerative medicine has in turn focused on how to engineer human cells for transplantation into organs as well as 3D printing [1-3]. In the rush to generate these stem cell therapies, most research aimed at the generation of one cell type or another from hESC or iPS cells has utilized chemical libraries or drugs to identify differentiating agents. What has been lost in this frenzy to find differentiating agents is the fact that an embryo produces all the differentiating factors required in order to create the ~200 cell types in the human body. Therefore, perhaps a better place to look for physiological differentiating agents is in the cells and tissues of the developing embryo. In addition to the autocrine and paracrine signaling within the developing embryo, hormonal signals might also be released from the endosalpinx (mucous lining of the fallopian tubes) during the journey of the zygote down the fallopian tubes until the attachment of the blastula to the endometrium, and later, from the placenta. These same autocrine, paracrine and endocrine signals allow for the continued replenishment (maintenance) of bodily tissues from resident totipotent stem cells throughout the course of life [4-6].

The hormonal signals and downstream molecular events that regulate the division and differentiation of the human zygote into a blastocyst during its passage through the fallopian tube into the uterus, and differentiation of the blastocystic cells into all tissues of the body are now only just starting to be identified. This research direction was largely derailed with the advent of methodologies to culture ESCs and the flux of researchers from other fields into the area of stem cell and regenerative medicine. Early, pioneering research from the laboratory of John Hearn from the 1970’s through the 1990’s showed that hormones associated with maternal reproduction (hypothalamic-pituitary-gonadal (HPG) hormones) are responsible for the early proliferation and differentiation of human stem cells is perhaps not surprising given the known functions of luteinizing hormone (LH)/hCG, follicle stimulating hormone (FSH) and GnRH in cell proliferation and of activins and sex steroids in cell differentiation [5,13-15]. Our and other research has determined that the machinery to synthesize all the hormones of the HPG axis is present very early in embryogenesis, perhaps as early as the zygote. Indeed, activins, GnRH, LH, FSH and steroids are all expressed by intact follicles for example [16-27]. Moreover, as we have identified in the brain [6], a regulatory hormone feedback loop may exist at this early stage of embryogenesis.

The above information suggests that it might be easier to let nature teach us lessons on the signaling factors required during development rather than recreating the wheel. Determination of the exact physiological hormonal signals required for hESC differentiation could be achieved by examining changes in gene expression of differentiating and neighboring tissues during embryogenesis in vitro. Understanding these signals will be essential for the controlled regeneration of tissues ex vivo. Until that time, regenerative medicine will have to rely on a tissue’s own resident cells to provide the appropriate paracrine signals for transplanted stem cells, or for transplanted stem cells to signal via autocrine mechanisms to allow for the repopulation of a tissue with appropriate cell type. Nature will be our best guide to identifying such factors.

References


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