BT5130 - Tissue Engineering - Assignment 2

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Question - What factors in asymmetric division cause one cell to retain its stemness while the other differentiates to IPC?

Answer - The unique ability of stem cells to self-renew in quantity while also differentiate into other kinds of cells, is governed by various intrinsic (arising from within the cell) and extrinsic factors (cues from the cell's environment). Various pathways have been identified for renewal in different kinds of stem cells. In Embryonic stem (ES) cells, the widely studied pathway/network is that of Oct4-Sox2-Nanog protein network[1, p. 2]. Oct4 and Sox2 are transcription factors and they are necessary for maintaining pluripotency in vivo and in ES cell cultures. They co-operate to activate a lot of other genes' expression, including Oct4 itself and the Nanog protein. It has been observed that Nanog is also required for pluripotency and *Nanog*-deficient ES cells undergo spontaneous differentiation. The Oct4-Sox2-Nanog form a regulatory circuit that represses genes that induce differentiation and maintains pluripotency. Epigenetic modifications involving polycomb and trithorax complexes also help in maintaining the pluripotency. Loss of certain polycomb complex components might lead to the irregular expression of other developmental regulators, making the ES cells differentiate [2].

Hematopoietic stem cells are known to react towards morphogen gradients [3] established by decapentaplegic (DPP)/ Sonic hedgehog (Shh)/ Bone morphogenic protein (BMP) and so on. Notch signalling immortalizes hematopoietic stem cells and allows them to increase in number by self-renewal. BMP-4's concentration maintains re-population/ renewal in cells. These gradients act as an intrinsic factor for the decision towards differentiation/renewal [4].

In *Drosophila*, neuroblasts divide asymmetrically by segregating atypical protein kinase C to daughters fated to remain as stem cells and provides molecules such as Numb, Prospero, and Brat to the daughter cells that will differentiate [5]. Several other extrinsic signalling pathways play a role in the above processes. Stem cells in metazoans are found in a niche which aids in stem cell maintenance and function. Displacement of cells from the niche, as discussed earlier, could result in differentiation. In *Drosophila's* germline, a cluster of somatic cells secretes a factor- Unpaired which is required to maintain the stemness in spermatogonial stem cells. Also, the mitotic spindle fibre's alignment can determine the respective positions of the daughter cells with respect to the

stem cell niche, thereby determining which cell would retain the stemness and which wouldn't. This was observed in *Drosophila's* spermatogonial stem cells that self-renew asymmetrically with the spindle oriented perpendicularly to the hub cells (constituting the niche). The displaced cell is fated to differentiate [6]. In *C. Elegans,* the distal tip cells express GLP1/Notch ligand Lag2. This signalling promotes mitosis and suppresses the ability to differentiate. In the case of mammals, perivascular stromal cells play a critical role in self-renewal properties of HSCs as they express high levels of the chemokine CXCL12 (SDF-1) and stem cell factor (SCF) which is in turn required to maintain the stemness of bone-marrow HSCs. Osteoblasts are also involved in the HSCs maintenance, as ablation of them resulted in the loss of HSCs. Other growth factors such as BMP, the transcription factor PU.1 and so on, induce differentiation in a dose-dependent manner, i.e., high level of PU.1 induces differentiation to dendritic cells over macrophages over granulocytes. The extracellular signals regulating HSCs are described briefly by Wang and Ema [7].

In conclusion, there are various intrinsic and extrinsic factors that govern the fate of stem cells, whether to retain their stemness or to differentiate. If intrinsic, the daughter cells have different profiles right after dividing which suggests their fate, and during extrinsic specification, the daughter cells have similar profiles/ developing potentials which are later influenced by external factors.

References -

[1] S. Masui *et al.*, "Pluripotency governed by Sox2 via regulation of Oct3/4 expression in mouse embryonic stem cells," *Nat. Cell Biol.*, vol. 9, no. 6, pp. 625–635, Jun. 2007, doi: 10.1038/ncb1589.

[2] V. Azuara *et al.*, "Chromatin signatures of pluripotent cell lines," *Nat. Cell Biol.*, vol. 8, no. 5, pp. 532–538, May 2006, doi: 10.1038/ncb1403.

[3] L. I. Zon, "Self-renewal versus differentiation, a job for the mighty morphogens," *Nat. Immunol.*, vol. 2, no. 2, Art. no. 2, Feb. 2001, doi: 10.1038/84239.

[4] B. Giebel and I. Bruns, "Self-Renewal Versus Differentiation in Hematopoietic Stem and Progenitor Cells: A Focus on Asymmetric Cell Divisions," *Curr. Stem Cell Res. Ther.*, vol. 3, no. 1, pp. 9–16, Jan. 2008, doi: 10.2174/157488808783489444.

[5] H. Shenghui, D. Nakada, and S. J. Morrison, "Mechanisms of Stem Cell Self-Renewal," *Annu. Rev. Cell Dev. Biol.*, vol. 25, no. 1, pp. 377–406, Oct. 2009, doi: 10.1146/annurev.cellbio.042308.113248.

[6] M. T. Fuller and A. C. Spradling, “Male and Female Drosophila Germline Stem Cells: Two Versions of Immortality,” *Science*, vol. 316, no. 5823, pp. 402–404, Apr. 2007, doi: 10.1126/science.1140861.

[7] Z. Wang and H. Ema, “Mechanisms of self-renewal in hematopoietic stem cells,” *Int. J. Hematol.*, vol. 103, no. 5, pp. 498–509, May 2016, doi: 10.1007/s12185-015-1919-5.