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Stem cell ageing, replicative senescence, and tumorigenesis

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Ageing of the organism besides functional impairment of mature somatic cells may be a matter of impaired regeneration as a consequence of altered self renewal of stem cells. The latter is caused by endogenous (cellular) and systemic (humoral) factors. These factors can involve cell damage and repair mechanisms, altered differentiation and induction of transdifferentiation towards alternative stem cell differentiation pathways, and epigenetic changes causing silencing of important key signalling genes.

Both stem cells and somatic cells are subjected to genomic and proteomic damage which accumulates and leads to the induction of cellular fail safe mechanisms, e.g. apoptosis and replicative senescence. Thus the suppression of tumour development by such fail safe programs occurs at the cost of proliferative and regenerative capacity. Monogenetic models of progeria suggest that altered DNA repair can cause ageing and progeria syndromes. Both loss of function mutations of DNA repair enzymes as well as enhanced DNA damage due to an increased load of reactive oxygen species (ROS) initiate cellular fail safe programs, but could also promote tumorigenesis, if proliferative stimuli

overcome cell cycle control check points. There is recent evidence that quiescent stem cells can also accumulate damage because the quiescent state results in an attenuation of checkpoint control and DNA damage responses for repair or apoptosis. Thus in spite of sufficient numbers of stem cells their regeneration capacity may be severely impaired. The cellular load of ROS is controlled by environmental and nutritional factors but also by ROS metabolizing enzymes, which also can be targets of polymorphisms and mutations. Thus active control mechanisms in cells are essential to maintain their genomic and proteomic integrity.

Age-related switching into preferred stem cell differentiation pathways can also augment the ageing process of an organism, due to the lack of specific functions of the resulting tissue. Augmented Wnt signalling was reported to drive muscle stem cells towards fibrosis rather than muscle regeneration. Preferred adipogenic differentiation of mesenchymal stem cells and adipogenic transdifferentiation of osteogenic precursors represent another similar scenario. Epigenetic dysregulation may be another hallmark of ageing where the

expression of growth and stemness factors can be impaired by DNA methylation processes and may also contribute to alterations of differentiation processes.

Adult and embryonic stem cells are both discussed as tools for cell based therapeutic strategies. Cell damage and ageing processes may occur during the ex vivo / in vitro handling procedures. Thus research on the maintenance of stem cell integrity appears to be extremely important. Strategies of differentially addressing healthy versus presenescent stem could be established to avoid forced proliferation of damaged cell populations. Exciting new data about a protective function of enhanced activity of the Arf/p53 (Cdkn2a locus (Arf) and p53) tumor suppressor pathway against ageing may promise that anti ageing protection can be even engineered in target stem cells to foster the security and minimize the risk of inducing malignancies in regenerative therapeutic strategies.

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