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ESC and iPSC DNA Repair Mechanisms

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Introduction

Compared to other somatic cells or terminally differentiated cells, embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) have very strict DNA repair systems that either reduce DNA damage or eliminate it through apoptosis. ESCs are isolated from the inner cell mass of the blastocyst stage during embryonic development, while iPSCs are reprogrammed from somatic cells using forced expression of stem cell master regulatory genes (Oct4, Nanog, Sox-2, c-Myc and/or Lin28, Klf-4) and have gene expression that is very similar to that of ESCs. Both ESCs and iPSCs are pluripotent, have a limitless capacity for self-renewal, and can develop into the body's three germ layers (ectoderm, endoderm, and mesoderm).

Pluripotent stem cells (PSCs) cycle and replicate DNA at a quicker rate (12-16 h) than somatic cells (24-36 h). Because of their brief cell cycle phases, DNA repair must be rapid and efficient to prevent the accumulation of mutations that could contribute to tumor growth.

PSCs have a very brief G1 phase, which prevents differentiation and increases cell proliferation, allowing pluripotency to be maintained. In contrast to somatic cells, PSCs have a short G2 phase and spend the majority of their time in the S phase [1-5].

Mechanism

If adequate repair cannot be accomplished in response to genotoxic and cytotoxic insults, cells experience apoptosis in a relatively short time (around 5-6 h). Apoptosis of PSCs is caused by an imbalance of pro- and anti-apoptotic proteins. Differentiation, which removes PSCs from the cell population, is another option for PSCs with greater DNA damage. PSCs spend the majority of their time (70%) in the S phase [4]. The expression/functioning of cyclins in the G2/M checkpoint is substantially different in PSCs than in somatic cells, and this can further increase the cell populations in the colony that have faulty mutations in the S phase.

In terms of p53 regulating DNA damage in PSCs, p53 independent apoptosis occurs after DSBs due to the lack of G1 arrest and cell senescence, but p53 deficient PSCs show high genomic instability, implying that p53 is required to maintain DNA stability and continue to be regarded as the genome's guardian. Low amounts of DNA damage can cause p53 to limit Nanog expression and push cells to differentiate (by downregulating Oct4, Sox2, and Nanog), effectively removing these PSCs from the main stem cell pool (depending on the extent of DNA damage). Because p53 suppresses iPSC formation, its levels must be carefully controlled (by Sirt1 triggered by Oct4). It is also required for maintaining pluripotency and monitoring DNA damage [2,3].

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Mechanisms of DNA repair

Nucleotide Excision Repair (NER), homologous recombination (HR), nonhomologous end joining (NHEJ), base excision repair (BER), and mismatch repair are some of the most frequent DNA repair processes (MR). Oct4, Nanog, Sox-2, and Sall4 are among the stem cell master molecules involved in cell cycle regulation, DNA damage response, apoptosis, and differentiation. PSCs often undergo apoptosis through the mitochondrial pathway if the damage is sufficiently severe, as cell senescence is not an option. When APRT/HPRT are injected into PSCs, they show lower mutational frequencies than differentiated cells, implying that PSC genomic stability is carefully regulated. During centrosomal amplification, PSCs have a higher number of supernumerary chromosomes than differentiated cells.

PSCs had a higher level of DNA repair genes related to double strand breaks (DSBs) and BER than somatic cells, according to a global gene expression analysis. Zscan4 is expressed in PSCs and aids in telomere elongation and HR. Due to double strand breaks, HR and NHEJ are the most widely used processes to address DNA damage, while ROS-induced DNA instability is managed by base excision repair and single stranded break repair. Antioxidant genes are also expressed at much higher levels in stem cells than in somatic cells. Depending on the stage of the cell cycle, several types of DNA repair mechanisms are used. HR repair occurs with great fidelity during the S/G2 phase of the cell cycle, and HR-related proteins stabilised by sall4 (RAD50, RAD51, RAD52, RAD54, MRE11, and NBS1) are enhanced when DNA replication damages are present. The phosphorylation of H2AX upregulates ATM, which improves signal amplification for DSB repair[4,5].

Repair mechanism in Pscs

The normal sister chromatid is easily available during HR repair to act as a template for repairing the damaged chromosome/lesion and replacing the altered DNA with the normal sequence. However, loss of heterozygozity (chromosomal segment duplication or loss of heterozygous allele) is a potential that could be more harmful than other DNA repair processes. Due to the longer S/G2 phase, HR is thought to be the principal repair mechanism in PSCs (to maintain adequate pluripotency regulation and stem cell self-renewal). When DSBs arise as a result of radiation (UV and IR), NHEJ repair takes precedence and involves DNA ligation at the ends of the DSBs, although there is the possibility of overhangs due to nucleotide addition or deletion. NHEJ repair proteins (KU70 and KU80, XRCC4, LIG4) can be activated at any time during the cell cycle because they do not require a typical template for repair, however they are most active during the G1/S phase. During PSC differentiation, NHEJ repair takes precedence. DSBs are more efficiently repaired in PSCs, with very little to no nucleotide loss/addition during repair, although somatic cells have a higher number of mutational frequencies [1,2].

Acknowledgement

None.

Conflict of Interest

The author reported no potential conflict of interest.

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