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THE ROLE OF p53-DEPENDENT AUTOPHAGY IN THE REGULATION OF PLURIPOTENT CELL BEHAVIOR

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Embryonic stem cells (ESCs) and their artificial counterparts – induced pluripotent stem cells (iPSCs) give rise to all differentiated cell types in adult organism. Therefore, pluripotent cells are an inexhaustible cell source for regenerative medicine. However, the successful clinical application of ESCs and iPSCs is hindered by the possible risk of teratoma formation upon transplantation of ESC derived products. As a rule, oncogenic potential is believed to be associated with the preservation of pluripotent cells resistant to differentiation among differentiated cells. For unknown reason under mitogenic stimuli these defective cells did not activate the mechanisms of exit from pluripotency and remained undifferentiated. In embryogenesis there are special mechanisms for eliminating the abnormal cells from further embryonic development that are massively initiated before gastrulation, the initial stage of cell differentiation into germ layers. It is known that autophagy plays a critical role in embryonic formation prior to implantation. Autophagy can be considered as one of the main cellular strategies aimed at large-scale restructuring of intracellular material after fertilization. It can be proposed that unless massive intracellular reorganization of embryonic cells occur effective, such cells will have defective proteostasis, affecting their differentiation potential. Therefore, the high level of apoptosis observed before gastrulation in embryogenesis is associated with elimination of mutant cells that are not suitable for differentiation. Damaged cells are marked with an activated p53 protein, indicating p53-dependent elimination mechanisms. And, apparently, the p53 activation mechanism is associated with damaged cellular proteostasis, regulated by autophagy. Based on the foregoing, p53-dependent autophagy can play a key role in determining the fate of pluripotent cells: induction of cell death and / or resistance to differentiation. In the present work, we showed that p53 protein is very close paired with autophagy and, under defective proteostasis p53 effectively induces autophagy-mediated cell death in pluripotent cells.

Keywords: embryonic stem cells, pluripotency, differentiation, autophagy, p53 apoptosis, AMPK, Ulk1, mTOR