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Aurka-to-p53 signaling: A link between stem cell regulation and cancer

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Researchers at Mount Sinai School of Medicine, the University of Manchester, and the MD Anderson Cancer Center have found a new role for an oncogenic signaling pathway in embryonic stem cell (ESC) self-renewal and in reprogramming adult cells into an ESC-state, which will aid in the development of future cancer therapies.

The findings promote the understanding of the self-renewal mechanism in embryonic stem cells and provide insight into the role of Aurka, an oncoprotein that is amplified in several human cancers. The research is published in the August 3rd issue of the journal *Cell Stem Cell*.

Embryonic stem cells (ESCs) and, more recently, induced pluripotent stem cells (iPSCs) hold great promise for biomedicine as a major source of differentiated cells for developing new ways to study disease etiology, the development of more effective drugs and diagnostic methodologies, and for future transplantation-based therapies. Cancer cells and ESCs can both proliferate indefinitely and show some similarities.

The researchers, a team at Mount Sinai School of Medicine led by Ihor Lemischka, PhD, Director of the Black Family Stem Cell Institute, in collaboration with groups at the University of Manchester and the MD Anderson Cancer Center, applied a functional genomics strategy and identified the protein kinase Aurora A (Aurka) as an essential component of ESC function.

These studies showed that Aurka functions by inactivating the well-

known tumor suppressor gene p53. The p53 protein acts as the "guardian of the genome" and mutations as well as deletions of the p53 gene are associated with a wide range of tumors.

In the absence of Aurka, up-regulated p53 signaling causes ESCs to differentiate and thus lose their stem cell state. By connecting the loss of Aurka to re-activation of p53 it was shown that Aurka adds a phosphate group (a process called phosphorylation) to a single amino acid in p53, thus shifting ESCs from a differentiation-prone state to self-renewal.

"These studies are exciting not only from a basic science point-of-view, but also because they suggest that stem cell research may impact the development of novel treatments for cancer. Conversely, cancer research may facilitate the realization of the biomedical potential of stem cells," said Dr. Lemischka.

Interestingly, in contrast to the low p53 levels in mature cells, this protein is highly expressed in ESCs and iPSCs. In addition, p53 has a limited role in promoting apoptosis – the process of programmed cell death – and cell cycle inhibition in pluripotent cells. The present findings provide a possible explanation to an unsolved mystery.

The study will aid in developing future cancer therapies and support the science underlying multiple clinical trials using Aurka inhibitors that are currently used to treat cancers.

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