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Reprogramming Cancer Stem Cells

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The Nobel Prize, recently assigned to Gurdon and Yamanaka for their solid and genial contribution to the reprogramming somatic cells for obtaining stem cells, underlines two important consequences for regenerative medicine and for alternative strategies in cancer therapy.

The use of reprogramming technologies have been developed to revert normal somatic differentiated cells (NSDCs), such as fibroblasts, into patient-specific induced-pluripotent stem cells (iPSCs) that can be easily differentiated into different lineages, potentially useful in cell therapy and regenerative medicine. The method invented by Yamanaka [1] allows inserting into the cell, by plasmid transfection, a set of four transcription factors (Oct4, Sox2, Klf4 and c-Myc) which have been demonstrated to be critical for staminality and cell differentiation [1]. Reprogramming methods have been progressively refined to be applicable to human cells [2], to increase their efficiency, to obtain a cell population easily suitable for differentiation [2], and to eliminate the use of viral plasmid, which could be responsible for unwanted side effects when used in personalized medicine [3]. These new methodological variations include the use of mRNAs encoding the above four transcription factors [4], a set of micro-RNAs [5] or a set of three lincRNAs (large intragenic non-coding RNAs) acting downstream of the canonical reprogramming transcription factors Oct4, Sox2 and Nanog [6].

In any case, this elegant technology will strongly contribute to resolve various scientific, clinical and ethical problems related to the stem cells. *First*, it demonstrated, by simply turning on the activity of a discrete set of genes, the reversibility of cellular identity after the morphogenetic differentiation and it demolished the dogma of the unidirectional and irreversible stability of gene expression associated with differentiation [7]. In addition, clarifying reprogramming mechanisms to pluripotency, it will reveal the pathways of lineage switching; this could simplify the *in vivo* differentiation from one lineage to another for clinical purposes [7,8]. *Second*, the publication of the landmark Yamanaka's paper has already made possible a number of potential clinical applications in different human pathologies. Somatic cells, such as fibroblasts, taken directly from the patient, can be reprogrammed to patient-specific iPSCs, overcoming all immune compatibility problems [7]. At present, diagnostic, therapeutic and pharmacological clinical applications are in progress in human hematologic, neuronal and other conditions where cell repair is necessary [3,9,10]. In addition, iPSCs can be obtained from patients bearing mutated genes responsible for monogenic or complex human diseases; such cells may represent a good experimental model to study a disease at personalized level [7,10]. *Third*, in the past the use of embryos as a source of pluripotent stem cells have raised many ethical controversies; the possibility to use adult autologous somatic cells to have stem cells for any differentiated lineage circumvented most of bioethical concerns on stem cell research and their use in humans [3].

Cancer Stem Cells or Differentiated Cancer Cells can be, at least in principle, reprogrammed into IPSCs, apparently showing a normal phenotype, utilizing the same four factors used for adult fibroblast or other somatic cell reprogramming [11].

Reprogramming of cancer cells have three basic aims: 1- to induce IPSCs that can be differentiated into any cell type for stem cell therapy, for preparing cancer vaccines or for pharmacological screenings; 2- to explore the possibility to normalize *in vivo* the malignant phenotype, as an alternative to the present therapeutic protocols; 3-to yield a larger cancer stem cell population, available for experimental manipulation, such as personalized model of disease, and exploration of their biological properties to attack resistant tumors and reduce relapses even in individual patients.

Different groups have reported the reprogramming of a number of solid tumors and derived tumor cell lines, both from humans and animals. Human Gastric cancer [12], leukemia, B lymphoma, melanoma, glioblastoma [13], sarcoma [14], mammary ca, prostate ca [15], and mouse embryonic ca have been reprogrammed with different technologies, although using all or some canonical genes, originally used by Yamanaka, with/without the addition of Nanog and Lin28. Despite in all cases biological behavior and markers typical of embryonic stem cells were evidenced, reprogrammed cancer stem cells displayed important differences in inducing pluripotency and thereafter in the possibility to obtain well differentiated cell lineages. More importantly, it seems that in all cases c-myc is necessary to obtain an advanced reprogramming; considering the oncogenic potential of such gene, this imposes a big limitation on the *in vivo* use of tumor iPSCs [14].

Zhang et al. [14] recently demonstrated that, reprogramming sarcoma cells using the four canonical genes plus Nanog and Lin28, cancer cells lost their tumorigenicity, reduced their drug resistance, and dedifferentiated as iPSCs, similar to the normal mesenchymal stem cells that in turn can be differentiated into various lineages such as fibroblasts and hematopoietic lineages. In addition, they have shown that in their cellular model the expression of c-myc appeared reduced, being hypermethylated during the reprogramming process. Thus, epigenetically modifying a reprogrammed cancer cell could correct some malignant effects of oncogene activation and oncosuppressor gene inactivation, suggesting a novel strategy to control tumor progression.

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Three basic steps seem to occur during cancer stem cell reprogramming process: as soon reprogramming transcription factors are expressed, a quote of cells start to divide faster and to lose their differentiation characteristics; this is associated to the down regulation of typical somatic genes; finally, a reduced number of cells continue to overexpress the canonical reprogramming genes, establishing a lineage with pluripotent properties, gene expression and its epigenetic regulation.

In conclusion, the understanding of reprogramming cancer cells and their potential clinical applications are just at the beginning of a long story that could be full of good results but also could reserve disappointing surprises.

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