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Editorial

Reprogramming and cancer

A series of revolutionary experiments over the past six decades heralded a new era in pluripotent stem cell (PSC) research. From early somatic cell nuclear transfer experiments (also referred to as cloning) in frogs by Sir John Gurdon (Gurdon et al., 1958) in 1958 to the first mammalian clone, Dolly the sheep, created by Sir Ian Wilmut (Wilmut et al., 1997) in 1997, and from the first mouse and human embryonic stem cells (ESCs), developed by Sir Martin Evans (Evans and Kaufman, 1981) in 1981 and James Thomson (Thomson, 1998) in 1998, respectively, to the more recent induced pluripotent stem cell (iPSC) technology, pioneered by Dr Shinya Yamanaka, first in mouse (Takahashi and Yamanaka, 2006) in 2006 and shortly after in human (Takahashi et al., 2007) in 2007, these landmark discoveries – which have collectively been celebrated with two Nobel prizes in Physiology and Medicine in 2007 and 2012 – radically reshaped our view of cell identity and cell fate.

Alongside breakthroughs in the domains of fundamental PSC research, the modeling of genetic diseases and regenerative medicine, a more limited set of studies sought to harness PSC research and cell reprogramming technologies to advance our understanding of the malignant cell state. In this special issue of *Stem Cell Research*, we present 7 articles that chronicle the history and lay out the current state of the art and more recent advances in the use of nuclear reprogramming to study cancer.

We begin with an overview by Kim of past research demonstrating the resetting of malignant features and epigenome by nuclear reprogramming methods, such as cell fusion and nuclear transfer. This is followed by a contribution by Zhang et al., who review the use of human PSCs (hPSCs) and hPSC-derived organoids to model solid tumors for mechanistic studies in cancer biology and applications in drug discovery and biomarker identification. Three articles highlight the use of iPSCs in the study of hematologic malignancies. Donada et al. review iPSC modeling of inherited leukemia predisposition syndromes; an article by Reilly and Doulatov focuses on the modeling of the clonal evolution of myeloid malignancy with patient-derived iPSCs; and Spyrou and Papapetrou discuss insights into specific vulnerabilities of leukemia stem cells (LSCs) obtained from iPSCs derived from acute myeloid leukemia (AML) patients. Pang et al. and Mazuelas et al. then summarize past studies and describe recent advances in iPSC research for the study of two inherited cancer predisposition syndromes: Li-Fraumeni syndrome, an autosomal dominant disorder caused by germline *TP53* mutations and Neurofibromatosis Type 1, caused by inherited *NF1* gene mutations, which are, respectively, associated with high incidence of osteosarcomas or peripheral nervous system tumors.

As our readers will notice, the applications of reprogramming in the study of cancer broadly fall into two categories. The first is the development of genetically faithful models of cancer driver mutations or combinations of mutations or even complete cancer genomes. This can be achieved either by reprogramming primary cancer cells into bona fide iPSCs – effectively capturing the cancer cell' s genome into an iPSC – or by gene editing of ESCs or iPSCs to introduce specific cancer-associated gene mutations. Notably the resulting PSCs from either strategy are fully pluripotent cells with the cancer epigenome completely erased and reset to that of the pluripotent stem cell state. A second type of reprogramming studies centers around using reprogramming technology, i.e. forced expression of the Yamanaka reprogramming factors (and potentially additional ones), to convert cancer cells into cells with altered epigenetic states. These epigenetic states are less well-defined and variable among studies. The resulting cells may or may not retain the full cancer genome of the starting cells – which are either primary cancer cells from patient tumors or established immortalized cancer cell lines –, but retain at least some of the driver mutations of the original tumor. The somewhat "murky" reprogrammed states of these cells are not proper pluripotent states and do not fulfill stringent criteria of iPSCs, notably independence from the reprogramming transgenes – and are thus usually referred to as "iPSC-like". Their epigenome is also different from that of PSCs and retains features of the cancer cells the reprogrammed cells originate from. Their usefulness for cancer studies is that they present self-propagating, partially or completely immortalized cells that are epigenetically distinct from the starting malignant cells, and often also phenotypically distinct in their malignant potential from the original cells. Altered cellular phenotypes associated with malignant features in such reprogrammed tumor cells include proliferation, replating capacity, differentiation potential, invasiveness, colony-forming potential in solid or semisolid media, and engraftment potential in xenograft animal models. Although both of the approaches to cancer modeling described above are valuable, they must be distinguished from one another, as they each provide different types of models that serve different purposes and are likely suitable to address different types of questions in cancer biology. Thus the need to adopt clear language and broadly accepted nomenclature when referring to these distinct types of cells, importantly distinguishing between PSC and PSC-like de-differentiated states, is paramount to progress in this field.

The cancer reprogramming field is now at a new turning point. The democratization of reprogramming technologies, in particular iPSC technology that is now more widely available to cancer researchers, has renewed the promise of nuclear reprogramming and iPSC models to inform cancer biology and precision medicine (Papapetrou, 2016). iPSCs can already provide faithful models of specific cancer driver mutations or entire cancer genomes that can help elucidate the pathogenesis and investigate the cell type of origin of specific cancers, aid

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target identification and validation, as well as drug testing and drug discovery. With welcome future developments to improve the efficiency of reprogramming of malignant cells and better define the reprogrammed malignant epigenetic states, cancer reprogramming can provide a powerful platform technology in cancer biology and oncology.

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