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Review

Application of induced pluripotency in cancer studies

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ABSTRACT

As soon as induced pluripotent stem cells (iPSCs) reprogramming of somatic cells were developed, the discovery attracted the attention of scientists, offering new perspectives for personalized medicine and providing a powerful platform for drug testing. The technology was almost immediately applied to cancer studies. As presented in this review, direct reprogramming of cancer cells with enforced expression of pluripotency factors have several basic purposes, all of which aim to explain the complex nature of cancer development and progression, therapy-resistance and relapse, and ultimately lead to the development of novel anti-cancer therapies. Here, we briefly present recent advances in reprogramming methodologies as well as commonalities between cell reprogramming and carcinogenesis and discuss recent outcomes from the implementation of induced pluripotency into cancer research.

1. Introduction

Induced pluripotent stem cells (iPSCs) are somatic cells that have been reprogrammed to form undifferentiated stem cells.[1,2] Direct dedifferentiation of somatic cells with enforced expression of pluripotency markers was for the first time reported by Takahashi and Yamanaka in 2006.[1] Since then, the utilization of iPSC technology has grown exponentially together with advances in reprogramming methodologies using a variety of pluripotency-inducing factors and delivery systems (presented below). Induced pluripotency was used to reprogram diverse types of cells, paving the way for dedifferentiation of transformed cancer cells. Currently, most human models of cancer are based on cancer cell lines and/or xenografts of primary tumor tissues cultured *in vitro*, reflecting the advanced state of tumor progression from which the cells were derived.[3] Due to the application of induced pluripotency,

Abbreviations: CSC, cancer stem cells; iPSCs, induced pluripotent stem cells; iCSCs, induced cancer stem-like cells; SCNT, somatic cell nuclear transfer.

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cancer research acquired a new turn. Utilization of iPSC technology in cancer studies gives the opportunity to elucidate the mechanisms which underlie the stages of cancer development. Moreover, the reprogramming of cancer cells gives rise to a population of cells that possess cancer stem cell (CSC) characteristics[4] – thorough exploration of their biological properties may help in better understanding of therapy resistance and tumor relapse. Also, the application of iPSC technology to dedifferentiate cancer cells creates a powerful tool for distinguishing epigenetic and genetic alterations that occur during tumor development and progression. In this review we briefly present recent advances in reprogramming methodologies as well as commonalities between cell reprogramming and carcinogenesis and discuss recent outcomes from the implementation of induced pluripotency technology into cancer studies.

2. Somatic cell reprogramming to pluripotency

Since the first discovery that fully differentiated somatic cell could be reprogrammed to become induced pluripotent stem cell (iPSCs), numerous methods have been developed to generate iPSCs.[1,2,5] Systematically improved strategies resulted in more efficient reprogramming (yielding a higher number of pluripotent colonies), and/or the generation of xeno-free iPSC lines lacking integration of any vector sequences into their genomes. The basal protocol established by Takahashi et al.[1,2] centers on the ectopic expression of master reprogramming factors (Oct-3/4, Sox2, Klf4 and c-Myc; OSKM) and epigenetic reactivation of endogenous pluripotency genes. In further studies reprogramming without the proto-oncogene c-Myc has been proposed either by using only 3 reprogramming factors[6] or by replacing c-Myc with less critical genes such as L-Myc or Glis1.[7–9] It was further demonstrated that in inducing pluripotency, the number of reprogramming factors could be reduced (to two factors Oct-3/4 and Klf4 or c-Myc) when using somatic cells that endogenously express appropriate levels of complementing factors.[10,11] Moreover, the emerging strategies of reprogramming were oriented to increase the safety of iPSC derivation; therefore, majority of them utilized transgene-free methods of reprogramming factors delivery to the host cell.[12] Integration-free mouse and human iPSCs have been generated using adenoviral vectors,[13,14] Sendai viruses,[15–17] Cre/loxP system,[18–20] the piggyBac system,[21,22] episomal vectors,[7,23,24] expression plasmid vectors,[25] small-molecule compound distribution[26–28] and direct mRNA[29,30] or protein delivery.[31,32] Examples of specific methods that have been recently utilized to reprogram mouse or human somatic cells to induced pluripotent stem cells are summarized in Table 1.

3. Reprogramming and carcinogenesis

The connection between oncogenesis and induced pluripotency is commonly discussed by the fact that during the reprogramming, somatic cells acquire potential for unlimited proliferation and ability to self-renew – both are well known features of transformed cancer cells.[33] Also, induced pluripotent stem cells lack contact inhibition of proliferation[34] and exhibit high telomerase activity and telomere elongation.[35,36] These are also two essential characteristics of cancer cells that facilitate tumor growth. Moreover, iPSC and cancer cell metabolism are overtly similar, with metabolite levels directly influencing chromatin organization and transcription.[37] To promote rapid cell proliferation and duplication, induced pluripotent stem cells balance their energy with biosynthetic requirements, which results in a metabolic shift from oxidative state to a glycolytic state in pluripotency,[38] a feature shared with highly proliferative cancer cells. Furthermore, the core pluripotency genes involved in the reprogramming process also play a central role in tumorigenicity.[39,40] The cocktail of Yamanaka's factors[1,2] that enables the dedifferentiation of somatic cells to a stem-like state is composed of well-known oncogenes, such as c-Myc and Klf4,[41,42] or genes that exhibit high expression in various types of cancer, such as Oct-3/4 and Sox2.[43–46] Oct-3/4 was demonstrated to promote tumorigenesis and inhibit apoptosis of cervical cancer cells,[44] support drug-resistance of prostate cancer,[47] and play a crucial role in maintaining cancer stem-like cells in lung,[48] liver,[49] breast,[50,51] brain[52] and other cancers.[53,54] Similarly, Sox2 enhances the tumorigenicity and chemoresistance of cancer stem-like cells derived from gastric carcinoma,[55] and is required to maintain cancer stem cells in the breast,[46] bladder,[56] ovarian,[57] and other cancers.[58–60] The importance of the thorough understanding of somatic cell reprogramming for enforced expression of "pluripotency factors" is evident when we consider the proposed theory of cancer evolution from dedifferentiated cancer cell that acquire stem cell traits (so called, cancer stem cell).[61] Advanced analyses of this multistep process will be extremely helpful in the recognition of specific molecular changes that reprogrammed cells and, in parallel, cancer cells need to make to achieve stem cell state. These molecular or cellular modifications may serve as therapeutic targets in anti-cancer treatment.[62,63]

Similarities between iPSCs and cancer cells also encompass the overall gene expression pattern[64] and epigenetic status.[65] Reprogramming of somatic cells to iPSCs requires profound alterations in the epigenetic landscape. During the reprogramming, pluripotent stem cells acquire a unique epigenetic profile enriched for active chromatin modifications (including H3K4me3, H3K36me3, histone acetylation, and hypomethylated DNA)[66] which are frequently found within the regions of pluripotency-associated genes. Also, alterations in DNA methylation within cancer-specific gene promoters as well as aberrant responses to epigenetic-modifying drugs resembling those for cancer cells[65] were observed in induced pluripotent stem cells, suggesting that thorough exploration of mechanisms governing induced reprogramming may provide a significant insight into the origins of epigenetic gene silencing associated with human carcinogenesis.[67]

4. Generation of induced cancer stem cells (iCSCs)

Generation of induced pluripotent stem cells from both normal and malignant patient tissue could be used to model