

Inter Conversion of Somatic and Cancer Stem Cell: From Discovery to New Paradigm in Cancer Therapy

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Letter to Editor

Organ is composed of special type of tissue and cells. Deficits in functionality and number of particular cells lead to the development of various type of human disease such as diabetes, neurological disease, cardiovascular, hepatic disorder and cancer etc. In the world of chronic disease there is a need of new branch of medicine that might help in the regeneration of tired and failing organ system. Present scientific community is giving emphasis and hope that regeneration of tired and failing organ system which results into various disease and disorders, might be cured/mitigated by special type of cells known as stem cells.

Ernst Haeckel, a German biologist, used the term “Stammzelle” (German for stem cell) to describe the ancestor unicellular organism from which all multicellular organisms evolved [1,2]. Literature revealed that Haeckel used the term stem cell in two sense “unicellular ancestor of all multicellular organisms” and as “the fertilized egg that gives rise to all cells of the organism”. The concept of stem cells was established in the late 19th century. Embryonic cells became a concern for pathologists at the beginning of 20th century, attempting to explain tumor genesis. After 1950, early work on embryonic cells and tumors led to the modern stem cell research [3]. In early 20th century it was thought that cellular differentiation can only be a unidirectional process. It was believed that the mature cells were permanently locked into the differentiated state and cannot return to a full mature, pluripotent stem cell state. However, the question still remained whether an intact differentiated cell could be fully reprogrammed to become pluripotent. In 1962, John B. Gurdon shifted this paradigm by demonstrating that differentiated somatic cell nuclei had the potential to revert to pluripotency [4]. After a long period of about 50 years, a fundamental discovery was done by Yamanaka. First time he demonstrated that an intact differentiated somatic cell could be reprogrammed to become pluripotent [5]. In the very next year in 2007, Yamanaka and his colleague first time isolated human embryonic stem cells (ESCs) and generated induced pluripotent stem cells (iPSCs) from terminally differentiated somatic cells [5,6]. In his study he used four transcription factors (initially 24 factors) Myc, Oct3/4, Sox2 and Klf4, are known as Yamanaka Factors. Yamanaka and John Gurdon (his fellow stem cell researcher) were jointly awarded the Nobel Prize in Physiology or Medicine, in 2012 for the discovery “mature cells can be reprogrammed to become pluripotent”.

Although the discovery by Yamanaka opened up a completely new research field but there were a lot to do in the field. Further researchers improved the delivery mechanisms of pluripotency factors; identified the various transcription factors required for pluripotency induction in different cell types; identified small functional substitute molecules for transcription factors; standardized trans-differentiation experiments (exocrine-endocrine cells, fibroblast-myoblast cells, fibroblast-cardiomyocyte cells and fibroblast cells to neurons). By 2012 many reports described functional cell differentiation but in mid-2013, Takanori and Hideki successfully generated a 3D vascularized and functional organ (liver) from human iPSCs. This 3D structure was able to form functional vasculatures into liver tissue (where transplanted) and were also performed the liver specific functions such as production of

proteins and drug metabolism. This was the first report demonstrating the generation of a functional human organ from pluripotent stem cells [7]. Efforts are needed to translate this promising knowledge for the treatment of patients.

Cancer cell may produce cancer differentiation cells and cancer stem cells. Cells having self-renewal and differentiation property are known as stem cells. Cancer stem cell is different from cancer cells as they have both differentiation as well as self-renewal properties. Each cancer stem cell has potential to diversify again into different lineage of cancer stem cells by dedifferentiation process leading into the formation of heterogeneous tumor [8,9]. Cancer stem cell may divide symmetrical, asymmetrical or symmetrical self-renewal to produce a set of two differentiated cell, one differentiated and one cancer stem cell or two cancer stem cells respectively. Under normal condition the decreasing order of division type is symmetric>asymmetric>symmetric self-renewal. Due to chemotherapy or radiotherapy the sequence might change in the following decreased order symmetric self-renewal>symmetric>asymmetric. Self-renewal symmetric differentiation largely contributes to the resistance and reoccurrence of tumors [10]. It has been reported that CSCs have capability to invade and get involved in metastasis. For this property they are also known as the key metastatic players of tumors. Oncogenic Ras and its important downstream target Myc is known to initiate the malignant transformation in CSCs [11]. A balanced equilibrium between differentiated cells (committed to tissue lineages) and cells with stem-like characteristics is the basis for the proper development of multicellular organism. When the intrinsic factor (e.g. transcriptional and epigenetic) equilibrium of a stem cell disturbed either with the effect of cell microenvironment or due to mutation accumulation, the cell converts into cancer stem cell (CSC). A functional characteristic microenvironment known as “niche” is required in the form of habitat of certain cells with specific functions. Several factors such as immune cells, ECM components, hypoxia and pH etc. are known to regulate this microenvironment [12-14].

Stem cell research in therapy might be divided into two major streams first “use of stem cell property for the generation of retired or failed tissue” and second “targeting the cancer stem cells to prevent cancer relapse and to increase the efficacy of cancer therapy”. In the previous section of this article it has been mentioned that stem cell might be utilized for the regeneration of organs in case of chronic disease. In the last few years it has been demonstrated that cancer stem cells have

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special type of niche having hypoxia and decreased pH environment. They together produce and increase stemness, cell differentiation, angiogenesis, immunosuppression and chemo resistance in the niche and its neighbour cells [12,15,16]. It might be inferred that targeting the pathways involved in hypoxia condition, angiogenesis and double DNA break repair system in cancer stem cells would be a better strategy for selective targeting of these cells. It is hereby also recommended that there is more rapid research in stem cell application is needed to fight against devastating diseases such as cancer.

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