Short Commentary

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Asymmetric Cell Division in Cancer: A Curse or a Boon?

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Abstract

Asymmetric Cell Division (ACD) is an inherent attribute of a variety of stem cell lineages including Cancer Stem Cells (CSCs). ACD is an indispensable phenomenon required at multiple stages during the entire process of embryogenesis. ACD is tightly coordinated by the micro environmental cues along with the intrinsic and extrinsic cell fate determinants. The tactful balance between the self-renewing stem cell pool and the lineage-specific progenitor cell pool is achieved via ACD. Reports suggest that any perturbation during ACD may give rise to events of tumorigenesis. CSCs exploit the phenomenon of ACD to regenerate a heterogeneous tumor mass causing tumor recurrence.

Interestingly, recent studies highlighted that exploiting the mechanism of ACD in CSCs by augmenting the generation of differentiable lineage-specific progenitors can also be an effective therapeutic approach to treat cancer. In this review, we discuss that as an intrinsic nature of CSCs, ACD can be considered as a sinful phenomenon, whereas extrinsically manipulating the phenomenon of ACD can have a positive outcome in cancer therapeutics.

Keywords: Asymmetric cell division; Cancer; Cancer stem cells

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Introduction

Recent knowledge about stem cell fate and Asymmetric Cell Division (ACD) has been derived from studies in model organisms like *C.elegans* and *D.melanogaster* [1]. ACD is an evolutionarily conserved phenomenon used by both prokaryotes and eukaryotes to generate cellular diversity and govern cell fate. ACD generates daughter cells with distinct phenotypes and fates, while Symmetric Cell Division (SCD) gives rise to two equal-sized daughter cells with a similar fate.

The phenomenon of tumorigenesis is a multi-step process including cell division and cell diversification. ACD regulators, including the Par3/Par6/aPKC complex and the Gα-LGN-NUMA complex, play an active role in a context-dependent manner in cancer development.

The extrinsically governing, tumor microenvironmental, decides the fate of stem cell and progenitor cell in an asymmetrically dividing mitotic pair. The tumor niches provide inflammatory cytokines, exosomes and hypoxic conditions which indeed create a favorable microenvironment for Cancer Stem Cells (CSCs) enrichment. Moreover, the intrinsic determinants of ACD and SCD with CSC, seem too essential to be overlooked to critically understand tumor progression and design novel therapeutics to target cancer from the root [2].

Asymmetric cell division as a curse during tumor development

In-vivo, even a limited number of CSCs can induce tumor formation in immune-compromised mice via ACD. *In-vitro,* tumorsphere formation assays also revealed the potential of a CSC to give rise to an entire heterogeneous tumorsphere with the help of ACD. The dreadful phenomenon of cancer relapse from the dormant state is also derived by ACD of CSC [2,3]. CSCs isolated from multiple types of cancers exhibited asymmetric distribution of cell fate determinants like Numb or microRNAs like miR-34a.

On the contrary, cancer cells primarily divide through symmetrically differentiating division. The tumor microenvironment contains exosomes derived from cancer cells or cancer stem cells which further contributes to CSC fate determination [4].

Exosomes play an indispensable role in cell-to-cell communication among the heterogeneous cell types present in the tumor niche via sharing tumor-promoting factors and creating a pro-tumor microenvironment [5]. However, to date, the details about establishing ACD in CSCs are very unclear and poorly understood. A study by Bu *et al*. linked ACD with CSCs in the early stages of tumor development and events of ACD are compromised at the later stages of highly proliferating cancer or are overpowered by increased SCD in CSCs [6].

At this very naive stage of research dealing with ACD in CSCs, it is very difficult to come to a concrete conclusion about how to manipulate ACD in a positive way to treat cancer. Though we have miles to go before we sleep, and we are at a stage of a needle in a haystack, much more exploration is yet to be carried out regarding ACD in CSCs.

Asymmetric cell division as a boon in cancer therapeutics

The cell fate determinants like Numb and Trim32 are known for their potential to reduce the pluripotency of CSCs via degradation of stemness-associated factors and thus promoting differentiation. Differentiated CSCs are easy targets for both chemotherapy and radiotherapy. Several reports suggest that patients having a high Numb expression are more sensitive towards radiotherapy as compared to Numb low patients [7,8].

In mouse fibroblasts, Trim32 knockdown facilitates the easy generation of iPSCs [9]. Several microRNAs like Let7a which is regulated by the C-terminal domain of Trim32 (a E3 Ubiquitin ligase) suppress the stemness potential of stem cell lineages leading to their differentiation [10]. miR-34a which is positively upregulated by the tumor suppressor p53 also induces differentiation in undifferentiated cells by promoting ACD [11].

Designing drugs or small molecules or therapies which can trigger ACD by overexpressing the progenitor markers which are responsible for reducing stemness potential in stem cell lineages can be an effective therapeutic strategy in combating cancer stem cell survival.

Discussion

The role of ACD in homeostasis and in cancer relapse is an epitome of nature's ability to intelligently utilize the same phenomenon as a boon and a curse [12,13]. Homeostasis and cancer relapse are two extremely contradicting events but still dependent on a similar attribute. Stem cells and CSCs share more similarities than differences. Controlled regulation of events is strictly followed by stem cells whereas in CSCs, the balance and control on event regulation is disrupted [14,15].

However, the trick is to find the balance to control CSCs ability to exploit ACD for tumor regeneration. Advanced research is already being carried out to sensitize these CSCs and to target the tumor from the root to prevent relapse. Once we identify the trick, cancer can be considered as a 'chronic disease' and not a life threatening one.

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