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Division Manners Functions in Controlling Stem Cells' Renewal

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Background

The malignancies don't show up suddenly, the undergoing alternations are a long journey to go through. Cancer stem cells were blamed for tumor recurrence and resistance [1], while, how did these cancer stem cells (CSCs) emerge is still in the mist. We previously identified several suppressive miRNAs in tumor initiation and progression, such as let-7 family [2,3]. In our previous issue of oncotarget [4], we turned to focus on the role of miR-208a in breast carcinoma and its effects on breast cancer stem cells (BrCSCs). We identified the inverse correlation between let-7a and miR-208a first, and then the positive correlation between Lin28 and SOX2 as well as between LIN28 and β-catenin in breast cancer tissues. At the same time, LIN28, SOX2 and β-catenin protein were also correlated with tumor stage. Secondly, miR-208a was proved to promote self-renewal ability of BrCSCs according to ALDH1-based FACS sorting and continuously cultured mammospheres results. What's more important, we demonstrated that miR-208a and let-7 formed a feedback loop through SOX2/β-catenin, LIN28 and Dicer, which provided new insight into miRNAs regulations of miRNAs in cancer stem cells, rather than the traditional miRNAs to mRNAs mode.

The improvements of our research lied on two concepts: the relationships between miRNAs and target gene mRNA, between protein and protein, such as miR-208-SOX2/β-catenin, SOX2/β-catenin-LIN28, which could be confirmed by Dual Luciferase Receptor Gene Assay and Co-Immunoprecipitation respectively, needed further exploration; The effects on BrCSCs of miR-208a included in this article were self-renewal ability in vitro, as a result, experiments *in vivo* was necessary for clarifying functions of miR-208a on BrCSCs. However, the most crucial point is the effect miRNAs or other non-coding regulators exerted on stem cells' biology and the consequences of the certain regulations that former researches often neglected, but would be more attractive in future. Therefore, the division mode of BrCSCs altered by miRNAs attracted our attention.

The way stem cells divided affect a lot on stem cells number, but how the division manners influence the cells' renewal is still in debate. Carcinogenesis may arise as a consequence of adult stem-cell dysfunction, which fails to undergo asymmetric cell division (ACD) [5,6]. The fine regulations of stem cells allow themselves to self-renew and generate the differentiated cells, forming and maintaining mature tissues and organs. The uncontrolled symmetric division will expand the stem cells pool, and resulted in numerous cancer stem cells (CSCs) in tumor [7,8]. We reviewed the relationship between asymmetric cell division and the self-renewal ability of cancer stem cells, which are crucial to unravel the cell biological basis of tumorigenesis. We hypothesize that the asymmetric division will decrease the stem cell number, but are not good for chemosensitivity, which will influence the future studies and the strategies of anticancer treatments.

Introduction

Human tumors are heterogeneous group, containing slowly proliferating cancer cells that are resistant to common chemoradiotherapy, which could regenerate the tumor group. The treatments aiming to eliminate the stem cells will definitely help to curing cancer, yield diagnostic and therapeutic approaches [1].

Cancer stem cells

Tumorigenic transformation occurs in the immortal or repeatedly dividing cells more common, for malignances represent the final stage of a multi-step process, meaning cells should accumulate a critical number of harmful modifications before the end of their life. The multicellular organisms require a tight control of cell divisions to ensure a proper balance between differentiated cell and immortalized stem cells in different populations, and numerous mechanisms preventing cancerous over-proliferation evolved. Cells can only escape jail control after having acquired a series of deleterious actions, which are really hard for the long procedures.

The occurrence of cancer was thought to be from one mutant progenitor cell, which generates the whole tumor group, and the progenitor cancer cell could either self-renew or differentiate into proliferating cells [9-11]. The cancer stem cells (CSCs) were the root of tumor recurrence, silently staying at G0 stage, and the general chemotherapies could only kill the fast proliferating cells. The CSCs will escape from multi-chemotherapeutic treatments, resulting in clinical failure and tumor relapse. The elimination of the CSCs will help to cure patients with cancer.

Defective ACD contributes to tumorigenesis and progress

The consensus definition of a CSC is a cell within a tumor that can self-renew and form the different cell types present in the tumor origin [1]. Cancer stem cells are capable of forming all the cell types that compose the tumor group. They divide throughout the life of the tumor to expand the stem cell pool, which then promote the tumor growth, metastasis and generate the chemotherapy resistance. In many instances, the division of a normal stem cell gives rise to one new stem cell and one differentiated cell, which help to limit the number of stem cells and ensure the normal organ function [8,12]. However in cancer stem cells, the oncogenic transformation gives rise to enormous CSCs through stimulation of symmetric cell division (SCD). The amplification of stem cell number will produce countless cancer cells with infinite proliferative potential, causing hence the excessive

production. Alternatively a second possibility could be that the normal stem cells accumulate mutations that allow them to divide symmetrically [8,13], perturbing cell polarity can cause neoplastic emergence through losing control of self-renewal ability of CSCs. MiRNAs inhibition on self-renewal were confirmed in our previous studies, but the possible functions of miRNAs in division manners still need to be explored, and the roles of miRNAs in stem cells division, or cells polarity in another way, will open another gate for miRNAs exploration.

Cell fate determinants in the control ACD

The aim of ACD is to create two different daughter cells; one is to sustain the stem cell group, and another is to differentiate into. The way to achieve this is the asymmetric segregation of cell fate determinants, such as Numb, PKC, p53 and so on [14-17], which could instruct the cell that inherits it to adopt a certain identity [8]. Our ongoing program also identified the crucial roles of ITCH, CCAT1 and other miRNAs sponges in regulating the division manners of stem cells. The asymmetric distribution of cell fate determinants makes cells segregate in a polarized way, with the mitotic spindle enriched asymmetrically. The influences on ACD decrease the stem cell number, determining the stem cells fate.

The CSCs concept puts the spotlight of cancer research on the factors that regulations of stem cell renewal through induction of asymmetric cell division. The direct interactions between FBW7, Numb and p53, or individually, all proved the suppressive functions of tumor suppressors were achieved by interfering the division mode [18,19]. Numb inhibited the MDM2's E3-Ubiquitin-ligase activity by forming a trimeric complex with MDM2 and p53, preventing the p53 degradation, and p53 is a strong factor of cell polarity induction [20]. What's more, the protective activity of Numb exerting on p53 was independent of Notch, which stimulates malignancy through promoting self-renewal of cancer stem cells [21-23], indicating the stronger anticancer effects of Numb through promoting ACD. Unpublished data of our group indicates that cyclin D1 regulated Notch intracellular domain (NICD) was controlled by certain suppressive miRNAs.

Controversial studies on asymmetric division related stem cells inhibition

Stem cells undergo ACD are therapies resistant

Asymmetric cell division produces less stem cells than those divided symmetrically; however, the cells underwent ACD are much steadier and may be resistant to therapies induced cancer inhibition. In one hand, for example, Akt was proved to induce the SCD of breast cancer stem cells in studies using ROSlow and ROShigh model, with MK167, H3K9me2 and MCM2 overexpressed in symmetrically divided stem cells [5]. The inhibition of Akt produced more G0-like cancer stem cells through promoting ACD. In ACD, one daughter stem cell differentiated into proliferative stance, which possesses $H3K9me2^{high}$/$HES1^{low}$ status, with diffuse Akt expression in divided cells. Another is a G0-like stem cell ($H3K9me2^{low}$/$HES1^{high}$), with intense nuclear localization of Akt expression [5]. Further, they found that Akt-1/2i induced asymmetric division more potently when first delivered to cells before mitosis, influencing the self-renewal capacity. In another hand, slowly cycling G0-like stem cells were enriched after cytotoxic treatment *in vivo*. Ipsita et al. in Massachusetts General Hospital examined the matched tumor biopsies obtained from patients who were given neoadjuvant chemotherapy before definitive surgical resection, and found the cells with MCM2low/H3K9me2low/HES1high/Aktlow (G0-like stem cells) were rare in pretreatment biopsies; however, these cells were enriched after treatment in matched biopsies [5], and these cells were not sensitive to anticancer treatment.

Different strategies should be applied in the process of clinical treatment

The suboptimal dose of anticancer reagent may cause asymmetric division instead of cell apoptosis, which will survive through clinical chemotherapies, and eventually reenter the cycle, proliferate and differentiate to form the new tumor group, resulting in tumor recurrence. This is not we desired in clinical practice. The elimination of cancer stem cells will be beneficial for curing tumor, and we previously thought that the increased ACD of stem cells helped to achieve this goal. However, in the case we discussed in this article, the control of stem cell number may be not good for the sensibility of chemotherapies. The limited CSCs are powerful and potential roots to regenerate the whole tumor. Therefore, at the first stage of clinical therapy, we should aim to decrease the stem cell number by induction of ACD, and then, the strategies should be turned to induce more cell death by using different strategy or reagent. Also, different concentration of anticancer reagents may function in different way, as we discussed in this paper.

Conclusions and Implications

Cancer possesses mutations that impair the capacity of normal cells responding to the signals that regulate proliferation. However, the theory of cancer stem cells (CSCs) reversed this opinion, meaning that cancer could arise from a few cells that have the capacity to generate the numerous different cells types in a tumor. We discussed the mechanisms through which the CSCs may emerged, and paid close attention to the formation of different cell types through ACD and SCD, which are crucial to understand carcinogenesis from the visual of stem cells. ACD will decrease the stem cell population through inhibiting the self-renewal and then the blocking proliferating rates of cancer cells. We were determined to find new strategies and reagents to induce more ACD of cancer stem cells, and thought that the decreased stem cell population will definitely inhibit malignancy and prevent tumor recurrence. However, here we hypothesized that, through asymmetric division, the slowly proliferating "G0-like" progeny may emerge, that are enriched following chemotherapy in breast cancer patients, constituting the biggest obstacle in clinical therapy.

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Conflicts of interest

All authors implicated in this research declared that there are no conflicts of interest.

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