

The relationship between early embryo development and tumourigenesis

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Abstract

With the recent substantial progress in developmental biology and cancer biology, the similarities between early embryo development and tumourigenesis, as well as the important interaction between tumours and embryos become better appreciated. In this paper, we review in detail the embryonic origin of tumour, and the similarities between early embryo development and tumourigenesis with respect to cell invasive behaviours, epigenetic regulation, gene expression, protein profiling and other important biological behaviours. Given an improved understanding of the relationship between early embryo development and tumourigenesis, now we have better and broader resources to attack cancer from the perspective of developmental biology and develop next generation of prognostic and therapeutic approaches for this devastating disease.

Keywords: developmental biology • cancer • embryo • tumourigenesis

Introduction

Cancer is a special kind of disease in which a group of cells display uncontrolled growth and it represents a serious assault on our quality of life. Developmental biology is a branch of biology that covers the total development process from the zygote to the adult with special focus on the embryo, because the embryo is the most important subject of the developmental biology and is a transition between genotype and phenotype [1]. With the recent profound advances in the field of developmental biology, it becomes apparent that the development of early embryo shares many similarities with cancer development in terms of both biological behaviours and molecular basis. This important view will promote the intersection between developmental biology and cancer biology and has twofold implications. On one hand, it enlightens us to study cancer from the perspective of developmental biology, which may reveal brand-new diagnostic and therapeutic targets for cancer. On the other hand, it suggests that we may envision embryo development as a process of tumour initiation and progression and incorporate decades of accumulation of cancer research theories, paradigms and models

into our investigation of embryogenesis, thus enhancing our in-depth understanding of this crucial process in our life history.

Embryonic origin of cancer

By definition, cancer is a class of disease in which a group of cells display uncontrolled growth (division beyond the normal limits), invasion (intrusion on and destruction of adjacent tissues) and sometimes metastasis (spread to other locations in the body via lymph or blood). These three malignant properties of cancer differentiate them from benign tumours, which are self-limited, and do not invade or metastasis. Developmental biologists have considered cancer as a special vital phenomenon that is a product of the natural selection with respect to cancer cells, although the result of this selection is unfavourable for human health and normal development [2]. Modern developmental biology deals with the genetic

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control of cell growth, differentiation and morphogenesis, a process that gives rise to the formation of tissues and organs. Thus, cell differentiation is a key issue of developmental biology. Interestingly, to a large extent, tumourigenesis derives from cell differentiation as a result of the disruption of normal cell differentiation process that is controlled by gene regulatory networks consisting of oncogenes and tumour suppressor genes. These genes are important determinants in cell differentiation, and their mutations play a key role in tumour initiation and progression [3–4].

In 1892, the French biologists Lobstein and Recamier speculated the concept of the embryonic origin of tumours for the first time. Then in 1970s, Dr. Pierce proposed the theory ‘cancer, a developmental biology’ and pointed out that tumourigenesis concerned intimately with developmental biology in a large extent [5]. It was presumed that the tumour cells and embryonic cells had lots of similarities and tumourigenesis was because of continued proliferation of the intracorporeal embryonic cells. Later, Prof. Bush pointed out that the formation of cancer cells was the result of reactivation of repressed gene in the process of normal embryonic development. With the progress of molecular biology, tumour immunology, developmental biology and experimental embryology, accumulating body of evidence confirmed the correlation between the development of early embryo and tumourigenesis [6–7].

Williams *et al.* [6] performed nuclear transplantation experiments in which triploid *Rana pipiens* embryos were injected with LuckÉ tumour herpesvirus. Upon the comparison of the chromosome profiles between renal carcinoma that developed in one of these triploid embryos and naturally occurring diploid renal carcinoma or a diploid renal tumour maintained as serial anterior eye chamber allografts for over 7 years, it was found that the majority of recently transformed triploid Lucké tumour cells could provide donor nuclei suitable for the characterization of developmental potential, confirming that tumour cells and zygote both have the enantiotropy with each other under certain circumstances. Thus, from the view of developmental biology, tumour cells can develop into the type of embryonic tissue in a manner similar to the zygote and both of them have obvious similarities [8].

Early embryo development and tumourigenesis

Recently, considerable research has revealed the significant similarity between the development of early embryo and tumourigenesis in terms of biological behaviours such as migration and invasion [9], gene expression and protein profiles [10], signalling pathways [11–12], cell differentiation [13], the mechanism of immune escape [14], and so on.

Similarity in cell invasive behaviours

Implantation of the embryo is one of the greatest mysteries of reproductive biology. There are striking similarities between the

behaviour of invasive placental cells and that of invasive cancer cells. Murray and Lessey [15] proposed that cellular mechanisms used by the placental cells during implantation are employed by cancer cells to invade and spread within the body. Integrins and other cell adhesion molecules, extracellular matrix and matrix metalloproteinases all appear to be involved and are regulated by the complex endocrine, autocrine and paracrine milieu within the uterus. Angiogenesis is a common feature of both implantation and cancer spread. During angiogenesis, endothelial cells also use similar cellular mechanisms to digest the surrounding matrix, migrate and form new blood vessels. A better understanding of the maternal mechanisms to control this invasive behaviour may provide novel insights into the behaviour of metastatic cancer cells and lead to better methods to control their growth and spread within host tissues.

Similarity in epigenetic regulation

Another significant similarity between tumourigenesis and early embryo development is epigenetic regulation. In the presence of DNA damage such as double strand breaks, the follicle cells might withdraw their processes from the maturing oocyte whereas the somatic cells might block information appropriate to a differentiated cell, thus leading to a genome-wide demethylation in both processes of the early development and tumourigenesis [7,16–20]. Although genome-wide demethylation is observed in embryo and cancer, it is fantastic that the level of DNA methyltransferases [7,16–20] is actually very high in embryos [21] and tumours [22–23]. In addition, another common feature of early embryo and tumour cells is an increase in the expression and transposition of retrotransposons, probably as a result of global demethylation. Long interspersed nucleotide elements and endogenous retroviruses are normally silenced by methylation, however, they are activated in embryos and cancer cells [7].

Similarity in gene expression

As described in previous section, human preimplantation embryonic cells have similar phenotype to cancer cells. Both types of cells undergo deprogramming to a proliferative stem cell state and become potentially immortal and invasive [7]. Thus, it might be expected the same sets of genes are expressed in cancer cells as in these embryonic cells, especially genes involved in deprogramming, proliferation and undifferentiation. All of these genes would not, by definition, be expressed by normal somatic cells, which are committed to differentiation and senescence [7,16–20].

Monk *et al.* [7] found that three novel embryonic genes and the well-known OCT4 gene were expressed in human tumours but not in normal somatic tissues. Recently, Baudino *et al.* [24] reported

that oncogene c-myc was highly expressed in embryonic stem (ES) cells and yolk sac cells and it was essential for early embryo development. c-myc deficient ES cells were dramatically impaired in their ability to form tumours in immune-compromised mice. Therefore, c-Myc expression and function is necessary for both embryogenesis and tumorigenesis. Moreover, Wenzel *et al.* [25] demonstrated that knockout of the well-known tumour suppressor gene retinoblastoma (Rb) in mice resulted in embryonic development defects such as ectopic proliferation, apoptosis, and impaired differentiation in extraembryonic, neural, and erythroid lineages. Other important genes expressed both during embryonic development and tumorigenesis but seldom in normal cells include c-met, c-fms, c-kit, fgf-2 and src.

Similarity in protein profiling

It is well known that some proteins typically present only during foetal development are also found in adults with certain kinds of cancer and are called oncofetal proteins. These proteins have been demonstrated to play important roles in cancer, and therefore have been used as common biomarkers in early diagnosis, treatment and prognosis of a variety of cancers. At present, oncofetal biomarkers are mainly divided into four categories: proteins (antigen), carbohydrates, glycolipids and hormones. Among them, carcinoembryonic antigen (CEA) is the most widely used oncofetal tumour biomarker applied to clinical cancer diagnosis [26–27]. In addition, a range of other diagnostic oncofetal biomarkers have been identified including α -fetoprotein [28–29], squamous cell antigen [30–31], survivin [32–33], cancer antigen 199 [34–35], prostate specific antigen [36–37], tissue polypeptide-specific antigen [38–39] and human chorionic gonadotropin [40–41].

The expression of these proteins in cancer and during early embryo development has an extremely important implication regarding cell differentiation and proliferation. Furthermore, the examination of these oncofetal proteins in biological fluids and the corresponding tumour tissues has been proposed to explain the similar immunological mechanisms between the tumorigenesis and early embryo development. Tumour cells produce and release the proteins into the circulation, such as tumour associated antigens, sharing the same mechanism of immune escape with foetal development [11]. It was found that the maternal serum levels of three tumour-associated antigens CEA, CA 228 and CA 15–3 were elevated during the three trimesters of pregnancy in healthy women [42–43]. Dvorak *et al.* [44] reported that embryonic and cancer stem cells shared various markers of ‘stemness’ and utilized similar molecular mechanisms and signalling pathways to drive self-renewal and differentiation. The fibroblast growth factor 2 (FGF-2) pathway is one of the most significant regulators of human ES cell self-renewal and cancer cell tumorigenesis. In addition, some hormones, such as human chorionic gonadotropin (HCG) and thyroid-stimulating hormone (TSH), are produced during the early embryo development as well as in a specific number of tumour cells. The

similarity of the expressed protein between the early embryonic development and tumorigenesis suggests a direct link between tumorigenesis and early embryonic development.

Similarity in other biological behaviours

In addition to the similarities discussed earlier, there are other biological behavioural similarities between the tumorigenesis and early embryonic development such as (1) the metabolism of cancer cells is similar to some of the early embryonic cells, and the activities of specific enzymes and their isozymes in the tumour cells are also similar to those in the early embryonic cells; (2) the proliferation and differentiation mechanisms during the early embryonic development and in the tumour cells are similar, and the tumour cells and embryonic cells are both characterized by high rate of proliferation [24]; (3) the similarity of the immune escape mechanisms [26–28]; (4) the similarity of signal transduction pathways between the tumorigenesis and early embryonic development. The evolutionarily conserved developmental pathways, mainly Wnt, FGF, Notch, BMP and Hedgehog signalling, are indispensable for embryo development by orchestrating various aspects of cellular activities and morphogenesis [45]. Interestingly, recent evidence demonstrated that networking of Wnt, FGF, Notch, BMP and Hedgehog signalling pathways is crucially involved in tumorigenesis [46]. Thus, it is tempting to imagine a scenario in which tumour recapitulates these developmental signalling pathways to drive tumour progression (Fig. 1).

Conclusion

Although the link between embryogenesis and tumorigenesis has been hypothesized for more than a century, the striking similarity between early embryo development and tumorigenesis become to be appreciated only in the past decades, largely thanks to the overwhelming evidence provided by modern cancer biology and developmental biology. Tumorigenesis and embryonic development are directly linked and have relevance to each other [47–51]. It is important to point out that although the development of early embryo and tumorigenesis have lots of similarity, some of the mechanisms are quite different. For example, although cancer stem cells in tumorigenesis share many characteristics with normal stem cells in early embryo development, the progenies of normal stem cells eventually form mature cells, which may mark the completion of development process, whereas those of cancer stem cells form constantly dividing progenitor cells that do not fully mature and thus drive tumorigenesis. A more significant difference between the development of early embryo and tumorigenesis is that tumour cells are frequently marked by genomic

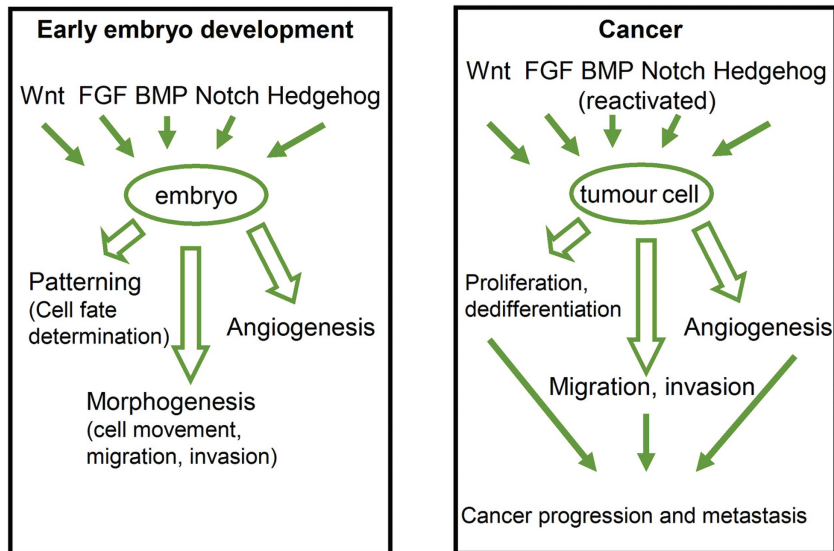


Fig. 1 Similar signalling pathways in early embryo development and tumourigenesis. Patterning and morphogenesis during early embryo development are co-ordinated by Wnt, FGF, BMP, Notch and Hedgehog signalling pathways (left panel). During tumourigenesis, these pathways are reactivated and contribute to cancer progression and metastasis (right panel).

instability that contributes to the activation of oncogenes and/or inactivation of tumour suppressor genes [4]. In contrast, the strictly regulated temporal-spatial expression of oncogenes and tumour suppressor genes that are essential for maintenance of stemness and development of embryonic cells are modulated by epigenetic but not genetic mechanisms.

Whatever the mechanisms, given the similarities between early embryo development and tumourigenesis as discussed earlier, now we have better and broader resources to attack cancer from the perspective of developmental biology. A typical example is the small molecule screening for Wnt/PCP signalling modulators based on zebrafish as a developmental biology model, which led to the identification of TNP-470 as the first small molecule capable of specifically inhibiting PCP signalling [52]. Interestingly, TNP-70 is an analogue of antiangiogenic natural product fumagillin, which provides further support that Wnt/PCP signalling is crucially implicated in both embryo angiogenesis and tumour angiogenesis [9]. We expect that more extensive small molecular

screening and genetic screening that target shared signalling pathways between early embryogenesis and tumourigenesis will contribute to the development of next generation of prognostic and therapeutic approaches for cancer.

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Conflict of interest

The authors confirm that there are no conflicts of interest.

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