World Scientific Research Journal Volume 6 Issue 9, 2020
ISSN: 2472-3703 DOI: 10.6911/WSRJ.202009_6(9).0001

The Relationship Between Embryonic Development and Cancer

Bixuan Wang[1, a]

[1]College of Life Science, Sichuan University, Chengdu, PR China.

[a]2017141241033@stu.scu.edu.cn

Abstract

With the development of developmental biology, accumulating evidence validate that embryonic development has a close connection with cancer. In this review, I briefly introduce the similarities between embryonic development and cancer, as well as the effects of embryos on tumor growth and the relationship between stem cells and cancers.

Keywords

Embryonic development, cancer.

1. INTRODUCTION

With the development of developmental biology, more and more evidence confirms that embryonic development is closely related to the occurrence and development of cancer. This is important because it can inspire the study of cancer from the perspective of developmental biology, deepen the understanding of the mechanism of cancer occurrence and development, and provide the possibility to discover new diagnostic markers and therapeutic targets for cancer. This article briefly introduces the similarities between embryonic development and cancer, the influence of embryos on tumor growth, and the relationship between stem cells and tumors, as well as the potential application value of these knowledge.

2. SIMILARITIES BETWEEN EMBRYONIC DEVELOPMENT AND CANCER

Developing organisms and cancers have some similar characteristics, including some key signaling pathways, epigenetic regulation, gene expression, protein profiling, and biological behaviors such as epithelial-mesenchymal transition (EMT).

2.1. Signaling Pathway

The precise spatial and temporal activation of developmental signaling pathways is required during embryonic development [1]. Some of these signaling pathways, such as Wnt, Hedgehog, and Notch, are also involved in tumor development.

The Wnt signaling pathway is involved in cell fate specialization, cell proliferation and cell migration during development [2]. The classic Wnt signaling pathway is active in almost all developing tissues, playing a crucial role in the formation of the body axis [3] and the maintenance of stem cell stemness [4], and it also plays a role in cancer. After Wnt binds to Frizzled receptor (Fz) and LRP5/6, LRP5/6 binds to Axin and GSK3, preventing APC, GSK3 and β-catenin from forming a complex. Free β-catenin enters the nucleus and acts as a transcription factor to promote the transcription of T lymphocyte-specific transcription factor (TCF) and lymphoid enhancer factor (LEF) [5]. Some targets of TCF/LEF promote cell growth and proliferation. Therefore, when this signaling pathway is over-activated, it will cause tumors. The Wnt signaling pathway has been recognized as a therapeutic target for various cancers [6].

ISSN: 2472-3703 DOI: 10.6911/WSRJ.202009_6(9).0001

The Hedgehog signaling pathway regulates gene expression associated with cell proliferation and differentiation [7], playing an important role in the development of many organs including the central nervous system, teeth and appendages [8], [9]. The Hedgehog signaling pathway is involved in the occurrence of one third of malignant tumors. Under pathological conditions, abnormal activation of the Hedgehog signaling pathway can lead to cancers such as basal cell carcinoma [10].

The Notch signaling pathway is also involved in the fate determination of embryonic cells and is essential for the development of many organs, such as the central nervous system, pancreas, bones, and heart [11]. Notch's role in tumor development is related to the microenvironment. It acts as an oncogene in some cases and as a tumor suppressor gene in other cases [12].

The TGF-β signaling pathway has a wide range of functions. It is the key to induce embryonic tissue growth and morphogenesis, and plays a crucial role in the EMT of embryonic development. It also plays an important role in the tissue homeostasis by inducing antiproliferative response and promote cell differentiation and apoptosis, becoming a tumor suppressor of early tumors [13]. The TGF-β signaling pathway can activate other downstream signaling pathways and trigger the secretion of cytokines, such asinterleukin-like epithelial-mesenchymal transition inducer (ILEI), which can induce EMT as well as the growth and metastasis of cancer [14]. Therefore, TGF-βmay be the potential therapeutic target of cancer.

Hepatocyte growth factor (HGF) can induce mitosis and morphogenetic during development and cancer [15]. HGF downregulates E-cadherin expression through the cascade of RTK and MAPK, which is closely related to cancer metastasis. In the HGF signaling pathway, the transcription factor Snail inhibits the expression of E-cadherin, and Snail is also the main factor that induces EMT [16].

The FGF signaling pathway can promote embryonic mesoderm differentiation by enhancing TGF-β signaling and mediate EMT through RTK [17], [18]. It also affect tumorigenesis through different mechanisms, including deregulation of cellular signaling, angiogenesis, and resistance to therapies. Therefore, FGF/FGFR targeted therapy is the focus of anti-tumor study [19].

The Hippo signaling pathway plays a central role in regulating organ size and tissue homeostasis from Drosophila to mammals. The abnormality of it, especially the abnormality of YAP/TAZ and TEADs, is a key factor in cancer development, and its effects include the induction of excessive cell proliferation, invasion, metastasis and drug resistance. Many studies targeting the key regulators of the Hippo pathway in cancer have been reported [20].

2.2. Epithelial-Mesenchymal Transition

During embryonic development, EMT performed by embryonic epithelial cells plays an important role in gastrulation and other developmental events. EMT also occurs during the spread of cancer cells. The transcription factors Snail and Twist, which play a role in gastrulation, are also drivers of EMT and metastasis in cancers such as breast cancer, pancreatic cancer, and colorectal cancer [21]. EMT acts on the migration of neural crest cells during development, facilitated by the transcription factors Snail, Slug and the Zeb family which are also associated with the invasion and proliferation of cancer cells [22].

2.3. Other Similarities

The same mechanisms used by embryo implantation are also used for tumor invasion and metastasis. There are also many similarities in the epigenetic regulation of embryos and tumors, with genome-wide demethylation, high level of DNA methyltransferases, increased expression and translocation of retrotransposons, and the activation of long interspersed nuclear elements and endogenous retroviruses which are usually methylated. Embryos and tumors are also similar in that they both express genes involved in proliferation and differentiation such as c-myc, Rb, c-met, c-fms, c-kit, fgf-2, and src. Embryos and tumors also have similarities in the

ISSN: 2472-3703 DOI: 10.6911/WSRJ.202009_6(9).0001

proteins they express, including a number of antigens, growth factors and hormones. In addition, embryos and tumors share similar mechanisms of metabolism, proliferation, differentiation and immune escape [23].

3. EMBRYO AND TUMOR GROWTH

Embryonic tissue can induce the differentiation of normal stem cells and tumor stem cells. Exposure of developing embryos to chemical carcinogens may cause malformations, but not cancer, suggesting that the embryo's microenvironment can correct carcinogen-induced mutations, thereby preventing tumorigenesis. The microenvironment of blastocysts controls the growth of transplanted malignant cells, and the factors secreted by blastocysts can induce the differentiation of cancer stem cells. In contrast, malignant cells transplanted to other parts of the embryo are uncontrolled [24]. The more differentiated tissue in the embryo can regulate the growth of cancer cells in it. Some tumors can be transformed into normal developing tissues in the appropriate embryonic microenvironment [25], [26]. Therefore, different embryonic microenvironments can make cells have different differentiation potentials and affect tumor growth, indicating that cancer is a developmental biology disease.

4. STEM CELLS AND TUMORS

Tumors and normal stem cells share some common features. They have some common signaling pathways, such as Wnt and Hedgehog. The genetic structure and metabolism of tumor cells are very similar to stem cells in that they have active proto-oncogenes, embryonic growth factors, carcinoembryonic antigen and anaerobic metabolic functions. The difference between tumor cells and stem cells is that tumor cells cannot complete development and differentiation due to mutations [24]. Tumor cells have specific membrane receptors that can be targeted by stem cell differentiation factors. Stem cell differentiation factors can induce the differentiation or apoptosis of tumor cells by correcting events that occur in malignant tumors such as mutations or epigenetic changes.

5. PROSPECT

Some evidence suggests that cancer is a developmental biology disease, which helps to understand cancer biology from a new perspective and promote research on the mechanism of cancer occurrence, invasion and metastasis, so that the growth and spread of tumor can be better controlled. Understanding cancer from the view of developmental biology also has great potential application value that could provide new strategies to treat cancer, promoting the development of new diagnostic markers and therapeutic targets. For example, key signaling pathways can be used as therapeutic targets, and the development of cancer can be inhibited by suppressing the expression of key genes in the pathway. The embryonic microenvironment may contain some factors that can inhibit tumor growth or induce the differentiation of tumor cells, which may be extracted and made into drug to assist in cancer treatment.

REFERENCES

[1] Slack JMW. Essential Developmental Biology. John Wiley & Sons, 2012.

[2] Loebel DAF, Watson CM, De Young RA, Tam PPL. Lineage choice and differentiation in mouse embryos and embryonic stem cells. Developmental Biology. 2003; 264: 1–14.

[3] Petersen CP, Reddien PW. Wnt signaling and the polarity of the primary body axis. Cell 2009; 139: 1056–68.

ISSN: 2472-3703 DOI: 10.6911/WSRJ.202009_6(9).0001

[4] Sokol SY. Maintaining embryonic stem cell pluripotency with Wnt signaling. Development. 2011; 138: 4341–50.

[5] Anastas JN, Moon RT. WNT signalling pathways as therapeutic targets in cancer. Nature Reviews Cancer. 2013; 13: 11–26.

[6] Dzobo K, Thomford NE, Senthebane DA. Targeting the Versatile Wnt/β-Catenin Pathway in Cancer Biology and Therapeutics: From Concept to Actionable Strategy. OMICS 2019; 23: 517–38.

[7] Briscoe J, Thérond PP. The mechanisms of Hedgehog signalling and its roles in development and disease. Nat Rev Mol Cell Biol 2013; 14: 416–29.

[8] Ulloa F, Briscoe J. Morphogens and the control of cell proliferation and patterning in the spinal cord. Cell Cycle 2007; 6: 2640–9.

[9] Zeller R, López-Ríos J, Zuniga A. Vertebrate limb bud development: moving towards integrative analysis of organogenesis. Nat Rev Genet 2009; 10: 845–58.

[10] Skoda AM, Simovic D, Karin V, Kardum V, Vranic S, Serman L. The role of the Hedgehog signaling pathway in cancer: A comprehensive review. Bosnian Journal of Basic Medical Sciences. 2018; 18: 8–20.

[11] Andersson ER, Sandberg R, Lendahl U. Notch signaling: simplicity in design, versatility in function. Development 2011; 138: 3593–612.

[12] 12 Aster JC, Pear WS, Blacklow SC. The Varied Roles of Notch in Cancer. Annu Rev Pathol 2017; 12: 245–75.

[13] Seoane J, Gomis RR. TGF-β Family Signaling in Tumor Suppression and Cancer Progression. Cold Spring Harb Perspect Biol 2017; 9. DOI:10.1101/cshperspect.a022277.

[14] Waerner T, Alacakaptan M, Tamir I, et al. ILEI: a cytokine essential for EMT, tumor formation, and late events in metastasis in epithelial cells. Cancer Cell 2006; 10: 227–39.

[15] Grotegut S, von Schweinitz D, Christofori G, Lehembre F. Hepatocyte growth factor induces cell scattering through MAPK/Egr-1-mediated upregulation of Snail. EMBO J 2006; 25: 3534–45.

[16] Birchmeier C, Birchmeier W, Gherardi E, Vande Woude GF. Met, metastasis, motility and more. Nature Reviews Molecular Cell Biology. 2003; 4: 915–25.

[17] Cordenonsi M, Montagner M, Adorno M, et al. Integration of TGF-beta and Ras/MAPK signaling through p53 phosphorylation. Science 2007; 315: 840–3.

[18] Moustakas A, Heldin C-H. Signaling networks guiding epithelial-mesenchymal transitions during embryogenesis and cancer progression. Cancer Sci 2007; 98: 1512–20.

[19] Ghedini GC, Ronca R, Presta M, Giacomini A. Future applications of FGF/FGFR inhibitors in cancer. Expert Rev Anticancer Ther 2018; 18: 861–72.

[20] Calses PC, Crawford JJ, Lill JR, Dey A. Hippo Pathway in Cancer: Aberrant Regulation and Therapeutic Opportunities. Trends Cancer Res 2019; 5: 297–307.

[21] Goossens S, Vandamme N, Van Vlierberghe P, Berx G. EMT transcription factors in cancer development re-evaluated: Beyond EMT and MET. Biochim Biophys Acta Rev Cancer 2017; 1868: 584–91.

[22] Cho ES, Kang HE, Kim NH, Yook JI. Therapeutic implications of cancer epithelial-mesenchymal transition (EMT). Arch Pharm Res 2019; 42: 14–24.

[23] Ma Y, Zhang P, Wang F, Yang J, Yang Z, Qin H. The relationship between early embryo development and tumourigenesis. J Cell Mol Med 2010; 14: 2697–701.

ISSN: 2472-3703 DOI: 10.6911/WSRJ.202009_6(9).0001

[24] Sell S, Nicolini A, Ferrari P, Biava PM. Cancer: A Problem of Developmental Biology; Scientific Evidence for Reprogramming and Differentiation Therapy. Current Drug Targets. 2016; 17: 1103–10.

[25] Postovit L-M, Margaryan NV, Seftor EA, et al. Human embryonic stem cell microenvironment suppresses the tumorigenic phenotype of aggressive cancer cells. Proc Natl Acad Sci U S A 2008; 105: 4329–34.

[26] Hendrix MJC, Seftor EA, Seftor REB, Kasemeier-Kulesa J, Kulesa PM, Postovit L-M. Reprogramming metastatic tumour cells with embryonic microenvironments. Nat Rev Cancer 2007; 7: 246–55.