Nuances in Developmental Biology on Cancer Development

Dr. K Chandra Mohan

Associate Professor, Department of Zoology, Yuvaraja's College, University of Mysore, Mysuru-570005, Karnataka, INDIA

E-mail : kcmycm@gmail.com

Abstract

It is now well known that the molecular pathways in embryonic development have similarities with the pathways of tumor development. Tumor development is a deterministic chaos with the genetic and/or epigenetic alterations in a differentiated mature organ.Further, the concept of cancer stemness originated from the thorough understanding of the molecular pathways from normal developmental processes. In this review, the molecular pathways that are common for the normal developmental processes and cancer development are being discussed, with the hope to establish the idea, that understanding the normal developmental genetic landscape is critical to understand the development of cancer and may help to develop novel anti-cancer therapeutics.

Keywords : Tumor, Cancer, mutation, gene regulation, signaling pathway.

Abbreviations : APC : Adenomatous Polyposis Coli, BMP : Bone Morphogenetic Proteins, EGF : Epidermal Growth Factor, GDF: Growth and Differentiation Factors, SHH : Sonic Hedgehog , TGFβ : Transforming Growth Factor β.

INTRODUCTION

Normal development

Embryogenesis starts with the formation of zygote through amphimixis of sperm and ovum, which results in the formation of blastula. The blastomeres are the new embryonic pluripotent stem cells derived from reprogrammed parental genome. The differentiation of pluripotent stem cells leads to organogenesis.

Our early understanding of cancer development started with the ultimate goal to understand the underlying mechanisms of cancer-causing gene mutations. Today, with the help of modern tools and techniques in cell biology, we have considerable understanding about cells and cellular mechanisms. Many genes that are already known for their role during embryonic development are now identified as hallmark genes for cancer development. For example,Wnt **(1)**, Hedgehog **(2)** TGFβs **(3)** Notch (**4**) and receptor tyrosine kinase pathways (**5***)* are extremely critical for normal developmental process.

All metazoans exhibit conserved Wnt signaling pathway, both during embryonic development and adult tissue homeostasis. Wnt proteins, secrete growth factors, which are known to regulate the proliferation and differentiation of progenitor cells, as well in repair of damaged cells **(6)**.Abnormal alteration of Wnt signaling in the embryo and in adults resulted in wide varieties of disease including cancer (**7**). Hedgehog signaling network incorporates many genes and proteins, which are known to regulate the transcription of many different genes depending on type of tissue (**8)**. Further, the Hedgehog pathway has been shown to regulate embryonic development including neural crest cell survival, left-right asymmetry, limbs patterning, development of eyes, bone, cartilage, muscle, nervous system, gonads and germ cells (**9**). The transforming growth factor β (TGF- β) belongs to the superfamily of growth factors. There are over 30 members TGF-β superfamily growth factors such as BMP (bone morphogenetic proteins), GDFs (growth and differentiation factors), Activins and nodal. These superfamily of growth factors are critical, in development and homeostasis of multicellular organisms. The ligands from TGF- β are known to regulate wide variety of cellular function like growth, adhesion, migration, apoptosis and differentiation (**10.11**)

Cancer Development

Cancer is a disease said to be caused by specific genetic alterations in the afore mentioned genes and their pathways which leads to uncontrollable division of cells without differentiation. This is in contrast to the embryonic development where precise spatio-temporal regulation of genes expression and development signaling pathways are executed (**12, 13**). Among the pathways described above, most frequently dys-regulated pathways are Wnt, Hedgehog and Notch pathways and they have been shown to participate in tumor initiation, maintenance and metastasis (**14**).Wnt signaling pathway components are Wnt co-receptors, β-catenin destruction complex, nuclear co-factors and Wnt secretory machinery. Wnt signaling pathway can be canonical (β-catenin dependent) or non-canonical (β-catenin independent) (**15**). The relationship between Wnt and cancer, arise from the finding that tumor suppressor protein such as adenomatous polyposis coli (APC) works in conjunction with β-catenin to regulate the Wnt pathway. The mutation in the APC protein has been documented in the colorectal cancer (**16**), hepatocellular carcinoma, endometrial cancer, and pancreatic cancer (**17**)

Many components of the Hedgehog signaling pathway have either tumor suppressing or proto-oncogenic in function. Thus, the proto-oncogenic become oncogenic when upregulated and concomitant tumor suppressors inactivation results in tumor growth. Inactivation of Hedgehog pathway during development results in congenital disorder whereas, the hyperactivation in the adult leads to tumorigenesis (**18**). Hedgehog pathway comprised of Hedgehog proteins such as Sonic, Indian and Desert; Patched receptor, Smoothened receptor, Kinesin protein, Protein Kinase A and GL1 transcription

factor. The hedgehog signaling pathway regulate the transcription of target genes via GL1 transcription factors (**19**). It has been shown that the mutation in the Hedgehog pathway promotes tumorigenesis and this correlation was first established in the tumors of skin, cerebellum and muscle as origin observed in the patients with Gorlinsyndrome (**20**). The extensive research work from the past decade revealed the abnormal activation of Hedgehog pathway in many tumors such as lung, liver, breast, prostate, stomach, colon and pancreas syndrome (**21**). Many studies have shown this is one of the dysregulated pathway in the cancer stem cells that have the capacity of self-renewal and differentiation (**22**)

The functional studies clearly linked the Notch signaling to oncogenic and tumor suppressive functions. Recent gene sequencing studies revealed the mutations in Notch genes and effects of these mutations in wide variety of cancer. In higher animals, there are four different Notch receptors and have EGF repeats followed by juxta membrane negative regulatory region and heterodimerization domain on the extracellular region. Whereas, the intracellular domain mainly consists of proline, glutamate, serine and threonine amino acids, typical components of the signaling pathway that regulates the gene expression (**23**). Alterations in Notch signaling molecules have been detected in many solid tumors. Within the cancer, Notch signaling pathway has been linked in the epithelial-mesenchymal origin, thus establishing mesenchymal phenotype that are hallmarks of cancer (**24, 25**).

While the mutations in the genes that are linked to normal development leads to cancer development, it is also important to realize the root cause of these cancer initiating mutations. The cancer causing mutations can be broadly classified as loss-of-function mutations (For eg.-mutation within tumor suppressing genes) and gain-of-function mutations (For eg.-mutation within oncogenes). Loss-of-function mutations are mostly point mutations or small deletions, chromosomal deletions or somatic recombination in which the normal gene copy is replaced by a mutant copy **(26**). On the contrary, if gain-of-function mutation occurs, it results in the new protein isoform with different functions compared to the normal counter part, and studies have shown these new proteins failed to fold into a tertiary structure.

Decades of research work suggest that there are multiple external as well internal genetic factors responsible for triggering cancer initiating mutations. For.eg., the external factors such as smoking on ling cancer, sun exposure and skin cancer, human papilloma virus (HPV) and cervical cancer and viral hepatitis, and hepatocellular carcinoma have been well established (https://www.cancer.gov/about-cancer/causes-prevention/risk).Whereas,the intrinsic factors refer to the basal mutation not influenced by the external factors and the intrinsic factors arise from random errors that happens during DNA replication. The error during the DNA replication is not just specific to humans, it occurs in different organism at different rates **(27).**

Conclusion

The knowledge about the genetic landscape of cancer development has been improving gradually and there is considerable understanding, as a result of decades of research across the world. It becomes evident and clear, that the genes responsible for causing cancer development are also known to have a direct role in normal development. Therefore, it becomes imperative to know the role of genes and their regulation in normal development as this holds the key to understand the development of cancer. This paves the way for novel drug development. In fact, there are several small molecules and large biologics (antibody based drugs) which are being developed and used in the clinical trials to curtail cancer development and in the treatment of cancer.

Acknowledgment

Dr.KCM gratefully acknowledge Yuvaraja's College, University of Mysore for providing facilities to carryout this research work.

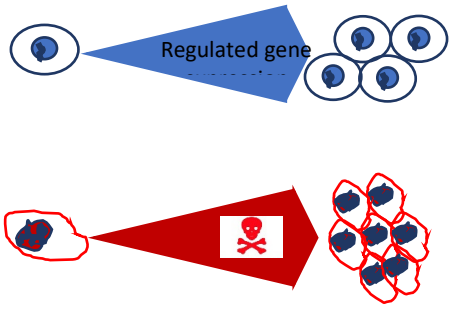

Figure. Contrast between normal development and cancer development. During normal development (top panel), the cells undergo asymmetric division and require balanced gene expression to promote the controlled normal development. Whereas in the cancer development (lower panel), the cancer-causing mutations disrupt the balance in the expression of the same genes that are involved in the normal development.

References:

1. Steinhart Z, Angers S. Wnt signaling in development and tissue homeostasis. Development. 2018 Jun 8;145(11).
2. Sanders TA, Llagostera E &Barna M. (2013). Specialized filopodia direct long-range transport of SHH during vertebrate tissue patterning. *Nature, 497*, 628-32)
3. Roth W, Wild-Bode C, Platten M, Grimmel C, Melkonyan HS, Dichgans J, Weller M. Secreted frizzled-related proteins inhibit motility and promote growth of human malignant glioma cells. Oncogene. 2000;19:4210–20).
4. Cormier, Sarah, Celine Souilhol, Charles Babinet, and Michel Cohen-Tannoudji. "Notch Signaling pathway and Early Mammalian Embryogenesis. "*MédecineSciences* 23 (2007): 26–8.
5. Localized surface activity of torso, a receptor tyrosine kinase, specifies terminal body pattern in Drosophila.*Casanova J, Struhl G. Genes Dev. 1989 Dec; 3(12B):2025-38*
6. Logan CY, Nusse R. The Wnt signaling pathway in development and disease. Annu Rev Cell Dev Biol. 2004;20:781-810.
7. Grainger S &Willert K (2018). Mechanisms of Wnt signaling and control. Wiley Interdisciplinary Rev Syst Biol med.
8. Cohen, M. Michael, Jr. The Hedgehog Signaling Network. American Journal of Medical Genetics 123A (2003): 5-28.
9. Abramyan, John. "Hedgehog Signaling and Embryonic Craniofacial Disorders." *Journal of developmental biology* vol. 7,2 9. 24 Apr. 2019.
10. Feng XH, Derynck R. Specificity and versatility in tgf-beta signaling through Smads. Annu Rev Cell Dev Biol. 2005;21:659-93.
11. Wu MY, Hill CS. Tgf-beta superfamily signaling in embryonic development and homeostasis. Dev Cell. 2009 Mar;16(3):329-43.
12. Slack J. M. W. (2006). *Essential Developmental Biology*. Malden, MA, USA: Blackwell Publishing Ltd.Aiello, Nicole M, and Ben Z Stanger. "Echoes of the embryo: using the developmental biology toolkit to study cancer." *Disease models & mechanisms* vol. 9,2 (2016): 105-14.
13. Aiello, Nicole M, and Ben Z Stanger. "Echoes of the embryo: using the developmental biology toolkit to study cancer." *Disease models & mechanisms* vol. 9,2 (2016).
14. Zhan, T et al. "Wnt signaling in cancer." *Oncogene* vol. 36,11 (2017): 1461-1473.
15. Clements WM, Lowy AM, Groden J. Adenomatous polyposis coli/beta-catenin interaction and downstream targets: altered gene expression in gastrointestinal tumors. Clin Colorectal Cancer. 2003 Aug;3(2):113-20.
16. Grigoryan, T., Wend, P., Klaus, A. &Birchmeier, W. Deciphering the function of canonical Wnt signals in development and disease: conditional loss- and gain-of-function mutations of beta-catenin in mice. *Genes Dev.* **22**, 2308–2341 (2008);
17. Harada, N. et al. Intestinal polyposis in mice with a dominant stable mutation of the beta-catenin gene. *EMBO J.* **18**, 5931–5942 (1999);
18. Kim, S. &Jeong, S. Mutation hotspots in the beta-catenin gene: lessons from the human cancer genome databases. *Mol. Cells* **42**, 8–16 (2019).
19. S Fattahi, MP Langroudi, H Akhavan-NiakiHedgehog signaling pathway: Epigenetic regulation and role in disease and cancer development, J Cell Physiol, 233 (2018), pp. 5726-5735.
20. M Varjosalo, J TaipaleHedgehog: functions and mechanismsGenes Dev, 22 (2008), pp. 2454-2472).

21. Niyaz M, Khan MS, Mudassar S. Hedgehog Signaling: An Achilles' Heel in Cancer. TranslOncol. 2019 Oct;12(10):1334-1344.
22. M Al-Hajj, MF Clarke, Self-renewal and solid tumor stem cells. Oncogene, 23(2204), pp.7274-7282.
23. Aster JC, Pear WS, Blacklow SC. The Varied Roles of Notch in Cancer. Annu Rev Pathol. 2017 Jan 24;12:245-275.
24. B. De Craene, G. Berx Regulatory networks defining EMT during cancer initiation and progression, Nat. Rev. Cancer, 13 (2013);
25. L.A. Timmerman, J. Grego-Bessa, A. Raya, E. Bertrán, J.M. Pérez-Pomares, J. Díez, *et al.*Notch promotes epithelial-mesenchymal transition during cardiac development and oncogenic transformation. Genes Dev, 18 (2004), pp. 99-115.
26. Chial, H. (2008) Tumor suppressor (TS) genes and the two-hit hypothesis. *Nature Education* 1(1):177).
27. Wu S, Zhu W, Thompson P, Hannun YA. Evaluating intrinsic and non-intrinsic cancer risk factors. Nat Commun. 2018 Aug 28; 9(1):3490).