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Review Article

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Cancer from Different Perspectives: Roaming in the Alleys of Developmental and Evolutionary Biology

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ABSTRACT

Our understanding of 'cancer' has evolved with scientific break-throughs, which provided insight into the pathogenesis of tumour progression. Oncology, in many occasions, has emerged as a field of interdisciplinary study, as multiple areas of cross-talks exist between the streams like developmental and evolutionary biology. This fact is often overlooked among medical professionals. The article tries to focus on epistemology of cancer research, the changing philosophy in a nutshell and a brief review of two broad domains of Biological Science; regarding how they have shaped our understanding of cancer.

Key Words: Cancer, Developmental Biology, Evolutionary Biology, Interdisciplinary study, Epistemology, Pathogenesis

INTRODUCTION

Let us begin from the authoritative work of Dr Siddhartha Mukherjeel,[1] which won the Pulitzer Prize in 2009, where the author has beautifully elaborated the changing discourses regarding our understanding of cancer. The disease regarded as 'The Emperor of all Maladies' in popular aphorism, as Mukherjee has described; was once an area of violent debate among academicians- regarding the identification of its true nature. Perhaps, fundamental of the understanding was the recognition that it is the aberration of normal or to be termed appropriately 'a distorted version of our normal selves'.[1] In the molecular era of cancer research, it was apparent that accumulation of non-lethal genetic mutations lie at the heart of carcinogenesis[2] and basically cancer is the clonal proliferation of a single cell that has acquired some genetic aberrations those give sufficient growth and survival advantage to propagate in an independent fashion.

The important point that is to be noted, this notion carries the echo of the fundamental cell theory proposed by Schleiden and Schwann, where it is stated, the life begins from a single cell in every living organism; - and that single cell, we know, is the precursor of embryo, the zygote. So, basically, a hint is hidden here that there exists some similarity between tumour biology and developmental biology. On the other hand, the origin of a full-blown tumour from a single cell reciprocates the idea of evolutionary transition from unicellular to multicellular organisms; that, we know, is the domain of Evolutionary Biology. The cross talks between developmental biology and Evolutionary Biology were pointed out long ago by Ernst Haeckel, as 'Ontogeny repeats Phylogeny'; where he argued the signature of the evolutionary process can be traced in the stages of developing embryo. And to some extent the developing embryo functions as a dynamic fossil of evolution.

With this brief introduction, we shall focus on some important aspects, those are shared by Tumour biology and Developmental biology; and then we will move to the arena of cross talk between pathogenesis of neoplasia and Evolutionary biology.

DISCUSSION

- **When the past haunts while looking back into the memories**
  There exist striking similarities between some tumours and phases of embryonic development, obviously the most important example will be the germ cell tumours.
- **Seminoma Testis/ Dysgerminoma ovary**- comprises the most primitive germ cells without any apparent differentiation[3]
- **Embryonal carcinoma**: mostly primitive germ cells with subtle predilection towards epithelial differentiation (as evidenced by positivity of Pan cytokeratin AE1/AE3)[3]

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- **Yolk sac tumour**: neoplasm of germ cells having potential for differentiation into both intra-embryonic and extra-embryonic structures,[3] like
  - Classic variant with Shiller-Duval bodies- simulates the secondary yolk-sac
  - Polyvesicular-vitelline pattern- mimics the allantois
  - Tubular variant- simulates developing gut
  - Hepatoid variant-simulates fetal liver
  - Mesenchymal variant-mimics spindle cell rich soft-tissue
- **Immature teratoma**- comprises germ cells with potential for differentiation towards intra-embryonic structures only.[3] The peculiar organoid pattern observed in Post Pubertal Teratoma of Testis, characterized by a lumen lined by primitive epithelium closely resembling mid-secretory endometrium with circumferential stromal condensation- is a marvellous mimicker of fetal organs in early stages of development.
- **Polyembryoma variant of testicular mixed germ cell tumour**- 'embryoid bodies' are noted in this scenario, which is identical to the early phase of developing embryo [3]
- **Wilm's tumour/ Nephroblastoma**- This triphasic tumour simulates the natural development of kidney showing the metanephric blastema in various stages of differentiation
- **Neuroblastoma, Ewing sarcoma/PNET**- contains rosettes which actually corroborates the developing neural tube.

Several examples may be given like Mesonephric carcinoma[4], Mullerian Papilloma,[4] sacral Chordoma (resembles developing notochord) and so on, which are strikingly similar to different regions of developing embryo. Literally, the forgotten past seems to haunt us, when we, the pathologists look deep into the histomorphology of these tumours.

Embryogenesis and Carcinogenesis:

• When The Pathways meet:

The cell signalling pathways important for embryological development are also one of the most commonly deranged ones; in case of neoplasia[5]. As for example:

- **Sonic HedgeHog Pathway:** The pathway important for left-right determination in embryonic disc[6] gets deranged in Basal cell Carcinoma and Medulloblastoma.
- **Notch signaling:** commonly deranged in T cell Acute Lymphoblastic Leukaemia, the Notch signaling pathway is necessary for maintenance of a stem cell pool amidst the differentiated tissue[6].
- **WNT Pathway:** The signaling cascade responsible for telencephalon development and early limb patterning[6], plays the key role in pathogenesis of colorectal carcinoma, Hepatocellular adenoma and Medulloblastoma.
- **Protease Activated Receptor pathway:** This is important for anterior-posterior cell patterning in early embryogenesis and regulation of microtubule dynamics.[6] Prostate carcinoma (with fusion of TMPRSS2-ERG) and the metastatic cancers show up-regulation of the PARs.
- **Bone Morphogenetic Peptide/ TGF-β/ SMAD-4 Pathway:** The signalling cascade playing important role in determining left-right asymmetry and responsible for distal limb morphogenesis[6], is dysregulated in cases of pancreatic carcinoma.

- **Common concepts followed: A tale of two Processes**
- **Epithelial to Mesenchymal Transformation (EMT):** Epithelial to mesenchymal transition is one of the fundamental concepts in embryogenesis. It is the key factor behind the formation of mesoderm, where the epiblast cells in the area of prechordal plate of primitive embryonic disc, transform and populate the intervening area between ectoderm and endoderm, thus forming the third germ layer[7]. Phylogenetically, it is also a landmark event, that is the sole basis of differentiation between Diploblasts and Triploblasts. The SNAIL and TWIST family of transcription factors are the master regulators of EMT.[2]

  Probably, the importance of EMT can be best delineated in the migration and homing of neural-crest cells. The neural-crest cells, are the precursor or postulated precursor of a wide variety of adult cell population, distributed throughout the body, starting from dorsal root ganglia, para-vertebral sympathetic chain, adrenal medulla to Schwann cells and melanocytes of skin.

  Maguire et al. has nicely elaborated the concept of EMT in the process of migration of neural crest cells.[8] Epithelial cells are characterized by cell-cell junctions with apicobasal polarity and are immotile. The first step in EMT is cadherin switch, where E-cadherin is down-regulated with sequential up-regulation of pre-migratory N-cadherin and then the mesenchymal cadherins 7 &11. SNAIL down-regulates the tight-junction proteins- occluding and claudin. Next, these cells start secreting MMPs and ADAMs to digest basement membrane and associated extra cellular matrix. The migratory neural crest cells express integrins for interaction with surrounding tissues.

  By the meantime, the para-aortic mesenchyme begins to secrete SDF-1, NRG-1 as a response to BMP-4 & BMP-7 generated by dorsal aorta, which directs the ventromedial migration of neural crest cells destined to form sympathetic ganglia and adrenal. These chemoattractant molecules act on receptors like CXCR4 and ErbB, and lead the cells to appropriate destination. Finally, the colonization of neural-crest cells is completed, when the Eph, Neuropilin and Robo receptors interact and recognize molecules like ephrin, sema-

phorins and slits expressed by residential tissue.

The above mentioned mechanism of migration of neural-crest cells is exactly similar, if not identical, to the mechanism of tumour metastasis. After homing in the metastatic organ, the tumour cells again undergo mesenchymal to epithelial transition, same type of transition is seen in metanephric blastema, when it differentiates into renal parenchyma.

- **Evasion of Host Defence:** The tumour cells often down-regulates HLA expression to evade immune recognition as a method of survival[2]. Classically, the same strategy is followed by intermediate trophoblasts during implantation, which do not express common HLA molecules, rather express HLA-G[7]; otherwise, the fetal graft would not be able to survive.
- **Importance of Tumour Microenvironment: Reciprocal signaling:** Now- a –days, it becomes apparent that the stromal cells are not passive bystanders in the context of tumour invasion, rather they actively participate and modulate its progression[9]. Both of them contribute to form the tumour micro-environment, the nature of which is being deciphered.

  Basically, same thing is true for tissue differentiation and morphogenesis during fetal development, where epigenetic mechanisms play a pivotal role.[2] It is solely regulated by reciprocal signalling or 'cross talks' between the developing tissue and the surrounding scaffold, which ultimately leads to organogenesis.
- **Cancer Stem cells:** The stem cells refer to a particular population of cells thriving in specific microenvironment of tissue (the stem cell niche), those have potential of self-renewal and asymmetric division (to another stem cell & a differentiated progeny) due to constitutive activation of telomerase.[2]

  The cancer stem cell hypothesis also postulates the presence of a particular population of neoplastic cells, which have maximal self-renewal property, are very much resistant for conventional therapy; and are responsible for recurrence of tumours in most cases.
- **Evolutionary Biology:**
- **Darwinian selection and multi-step model of carcinogenesis:**[2] Though the tumour arises from clonal proliferation of a single cell that carries a genetic aberration (the driver mutation), soon multiple clones arise from it, each of which harbours different newly acquired mutations (the passenger mutations). Especially, acquisition of a mutator phenotype highly accentuates the process. Each of these clones abides by the rules of classical Darwinian selection. In a stressful condition(as in case of chemotherapy), the favourable clone gets selected and the genomic landscape of the original tumour gets replaced by the selected clone. It explains the basis of chemoresistance to the previous regimen after recurrence. Basically, this phenomenon can be viewed as the unleashment of evolution in the 'fast forward' mode.

The model of multistep carcinogenesis has been criticized in recent past by Sottoriva et al., they proposed the big bang model of colorectal carcinogenesis instead.[10] They pointed out selective sweeps that significantly alter the clonal composition of the final tumour are extremely rare after transition to advanced tumour, owing to the dynamics and spatial constraint of rapidly growing population and formation of tumour microenvironment niches. Basically, the pervasiveness of a particular mutation depends solely on the time of its acquisition, not necessarily because they are 'selected' due to a possible survival advantage.

- **Evolution shaping cancer:** Evolution has tried to prevent emergence of & to constrain the activity of cells behaving in independent manner, otherwise the transition from unicellular to multicellular organisms were not possible; neither there would be existence of complex multicellular systems. This is exemplified by the highly efficient Tumour Suppressors and the extreme fidelity of DNA replication and Repair, both of which are evolutionarily conserved.[11] Onset of programmed cell suicide programme when the situation goes beyond repair, is another fundamental strategy.[11]

  It also makes perfect sense when recall that cancer is basically a disease of elderly, if we spare the domain of childhood tumours.[12] The Darwinian selection behind the stream of evolution, actually is bothered about the number of healthy progenies an organism can produce after proper accommodation in the changing milleu. In other words, it basically takes into account the incidents of life till successful reproductive cycles are ensured. So, evolution has tried to maintain stringent tumour suppressor mechanisms at least up to reproductive age, -whether it becomes deranged after that, is not at all a concern of evolutionary trends.
- **Peto's Paradox:** Based on the existing knowledge regarding cancer, it is likely that the organisms having greater number of cells, will have the greater probability to develop mutation in a cell, and thereby greater chance of developing cancer. However, it is actually not the case, which is known as Peto's Paradox. Mammals with higher body mass have developed potent mechanism of repression of Telomerase activity and induction of replicative senescence, like the elephants have evolved pseudogene duplications of TP53.[13]
- **Unfolding the tumour biology**
- **Speculating the cell of origin:** Identifying the cell of origin is one of the primary motives of the researchers while deciphering the pathogenesis of tumour. What lies behind the neoplastic transformation? Is it a dedifferentiation process of a mature cell? Or it originates from the resident tissue stem cells which becomes

dysregulated? Or it is a result of maturation arrest of a primitive cell line?

Most probably, all three mechanisms play role in different contexts. The notion of dedifferentiation is particularly demonstrated in cases of Liposarcoma.[14] Dysregulation of resident stem cells occur in case of CML (ample evidence is there that it originates from a multipotent hematopoietic stem cell); on the other hand, the phenomenon of maturation arrest is exemplified by the remarkable success of Iso-tretinoin in treatment of AML with t(15,17).[15]

- **Tracing the cell lineages:** Knowledge of tumour biology has enriched our understanding of developmental biology and vice versa. The best example will be the immunophenotype based classification of Lymphoma and corresponding developmental classification of B and T lymphocytes based on expression of cluster differentiation markers.[15](shown in the table below)

Table 1: Expression of different immuno-markers according to B cell type and the associated lymphoid neoplasms

B cell Type	Positive Immuno-marker	Associated neoplasm
Pro B	CD 34	Pro B ALL
Pre-B	CD34, TdT	Pre-B ALL
Immature B	No specific marker*, CD20±	
Mature Naive B	CD 20	Mantle cell Lymphoma
Germinal centre B	CD20, CD10, CD23	Follicular Lymphoma; DLBCL, GCB type
Memory B (marginal zone)	MUM1	DLBCL, ABC type
Plasma cell	MUM1, CD 138	Plasma cell Myeloma

*Except the pan B cell markers: CD19, CD79a, PAX5.

CONCLUSION

Tumour biology shares important similarities with Normal embryonic development, both morphologically and in underlying mechanisms. The difference lies there that one is strictly regulated while the other is not; - the feature was aptly pointed out by Kelher F C et al.[6] Knowledge of tumour biology has enriched our understanding of developmental biology and vice versa.

Evolution has tried to prevent emergence of & to constrain the activity of cells behaving in independent manner[12] and thereby influences tumour biology. The evolution of tumour cells needs to be explained by Darwinian Philosophy on the other hand.

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