GRT Journal of Education, Science and Technology

Published by GRT College of Education ISSN: 2584-301X

Cancer: intricacies, improbabilities and exceptions

A. Anbarasu[1], P. Karnan[2] and K. Ramalingam[3]

[1]Government Higher Secondary School, Chithathur, Tiruvannamalai-604410.

[2]GRT College of Education, Tiruttani-631209.

[3]Mediclone Biotech Research centre, Chennai-48, Dr.Rai Memorial Medical centre (Cancer Treatment and Research), I.E.C member.

Article History:

Received on: 27 Mar 2023
Revised on: 02 Apr 2023
Accepted on: 23 Apr 2023

Keywords:

Cancer, Improbabilities, Exceptions, Mutations, Oncogenes, Genome, Recapitulation.

Abstract

The disease cancer and the cancer cells are unique in exhibiting various intricacies and mechanisms which are exceptions and deviations to the normal developmental cues or regulations. Though the bottom lie for all cancers is the genetic mutations in the critical genes of the nuclear genome and mitochondrial genome the mechanisms involved in its development and growth elucidates the diverse atavistic features like the recapitulation of certain embryonic characters like rapid multiplication and prokaryotic resemblances, such as anaerobic existence like that of prokaryotes contact inhibition in the cluster of cells, expression of their gene incorporated into the patients genome, promotion of oncogenes expression through non-oncogenes viral genome incorporation etc. Even the cancer cells resistance to chemotherapy drugs and radiation is due to synthesis of resistant proteins similar to prokaryotic homologous tools

∗Corresponding Author

Name:A. Anbarasu

Journal Home Page : https://grtjest.com

Production and Hosted by
GRT College of Education

INTRODUCTION

Cancer is a disease of multiple etiology induced by innumerable intrinsic and extrinsic risk factors (Prognostic) which deviate a cancer tissue / cell from the general developmental cues and paradigms Ramalingam[1]. A perusal of literature on the biology of cancer cells would reveal that a cancer cell is an ultimate phenotype consequent to the chronic induction of etiologic factors and concurrently the accumulation of mutations in both the nuclear and mitochondrial genome of the cell Singh Pooja., Francies[2]. It is a process of disease manifestations due to chronic and persistent stimuli and the cumulative culminating responses by the cell. It also involves a series of biochemical reactions occurring in different phases due to both expression and suppression of genes of the repairable nuclear genome and the

irreparable mitochondrial genome and their epi-genetic expressions of a repertoire of proteins. Recently it has been reported that before a normal cell transforms into a cancer cell it may accumulate about one lakh mutations Chu et al.[3] or single nucleotide variations(SNPs). The voluminous changes that are discernible in the cancer cell genome sequences make the disease cancer unique and confer the title as "EMPEROR DISEASE" in human. Even gene therapy could not cure the disease in the modern therapeutic strategies of varied categories since cancer is not monogenic but multigenic.

The development of the disease cancer or the transformation of a normal cell into a cancer cell takes up the different profiles of initiation, transformation, proliferation, growth, invasion / metastasis, secondary development and death etc. represent a continuum inside the body of a patient taking a long latent period of 15-20 years, challenging every formidable reactions of the individual and overcoming all immunological surveillance and reactions of the host.

Understanding the various intricacies of cancer disease reveals that cancer cells deviate from the normal feature of cells where in the normal growth of the individual occurs due to the culmination of various physiological, biochemical and metabolic reactions, co-ordinate with other profiles of endocrines and immunological organs, abiding all the rules of the developmental process with no or little exceptions. On the contrary the development of cancer takes up an entirely different profile(s) where in the exceptions are the established rules here.

In normal embryological development and growth, the cells know by virtue of their positions what to do! and so differentiate as per the pre-determined pattern and sequence. The functions of homeotic genes in development are evidence Balinsky[4]. Similarly the concept of primary and secondary organizers by spieman and Mangold are evidences for the sequential development of organs. But in cancer development the cells abide the abnormal commands executed by the genomic alterations and proceed in a neoplastic pattern where there are no rules but only exceptions are the rules.

CANCER STEM CELLS: A DEVIATION CUM EXCEPTION

Former description of cancer stem cells is the number of fully viable proliferating, clonogenic cancer cells. However latter studies have revealed that in a tumour mass, about 0.8-1 percent of cells which are both chemo resistant and radiation resistant are to be called stem cells. The similarity between a normal tissue stem cells and cancer stem cells is that in the former the stem cells proliferate to reinstate the normal cells consequent to a tissue injury while in the latter the stem cells reinstate and repopulate the resistant cancer cells even after surgery, chemotherapy and radiation therapy. In a mass of malignant tissue, those cells nearest the blood supply, well oxygenated and well-nourished are most likely to survive and proliferate. These cells are killed by the cytotoxic chemotherapeutic drugs. However some anoxic cells acquire new immunological competence and survive as stem cells. These cancer stem cells express novel surface antigens different from other cancer cells and they become resistant to drugs and radiation injury, resistant to free radicals, provided with anti-apoptotic proteins and signals and represent the major contributor to the revival of cancer in distant organs through metastasis. These cancer stem cells remain a challenge to the various therapeutic strategies in the clinical settings until this hour.

Besides the above cancer stem cells, resistant cancer cells also contribute to the 10-30 percent of recurrence of cancer in patients after treatment. Such a recurrence was noticed both in the primary site and nearby lymph nodes and tissues as well as in distant organs. These 10-30 % patients are in possession of a muti-drug-resistance gene (mdr I) which are over-expressed to produce abnormally high levels of phycoprotein viz., p-gp which acts like a proton pump and expels the cytotoxic cancer killing drugs from the cancer cells and thus enable their devastation. Ramalingam et al.[5]

Among the biochemical constitutions white refined sugar in cancer patients provides the fuel for their cancer cells anaerobic glycolysis mechanism selectively. A Russian Scientist Dr. VlecdimirM.Dilam has adduced evidences to the of sugar / carbohydrate and cancer etiology. Sugar is a strong candidate perhaps a much stronger candidate than fat, and cancer cells feed on glucose rather than oxygen unlike normal cells.

Their energy metabolism being shifted to anaerobic side, all cancer patients may have high insulin and triglycerides to promote the Warburg's effect in their cancer cells to enable them to subsist on minimal energetic metabolism which could have been mediated through genetic "switch on" mechanism. This is again evidence to the recapitulation of embryonic characters or primitive prokaryote characters by the malignant cancer cells. This could be a tenable argument in view of the evolutionary descent of differentiated eukaryotic cells from the progenitor prokaryotic cells which respired anaerobically and subsisted in the reducing atmosphere of the archeozoic / Proterozoic era. Such genetic modulation in cancer cells may be an exception to their normal counterparts in the same patients body or the normal individuals. The above evolutionary shift in oxidative energy metabolisms and the reversal of genetic switch in cancer cells analogous to that of prokaryotes is a paradigm shift in its own right.

However cancer cells also exhibit aerobic glycolysis to synthesize the basic structures for their proliferation and growth. The above shunt of both aerobic and anaerobic respiration is a unique exception to the developmental cues and rules, in the cancer cells.

Cancer cells no doubt employ diverse mechanisms to promote their own self growth and proliferation and the mechanisms continue to operate until the cells arrive at the stage to undertake the deleterious Invasion to distant organs through metastasis, when the growth process and stepwise changes that are taking place inside a cancer cells.

All cancers tumours may be of benign nature in the beginning phase of differentiation, showing the typical normal cellular characteristics in their structures and such functional attributes as slow growth, low mitotic rate and index in contrast to the malignant neoplasm's which have acquired rapid growth, potential, a high mitotic index, consisting of undifferentiated benign plastic cells. The transition between the passive phase to the malignant state a plethora of both structural and functional aspects which include in broad category:

- Membrane level changes in the lipid moiety
- Cytoplasmic level changes involving specific receptors and messengers and molecular chaperones
- Organelles level alteration in the basic sequences of nucleotides
- Enzyme components to boost the metabolic profiles of cancer cells
- Epigenetic expression of proteins both at intracellular and extracellular milieu and lastly the anti apoptotic mechanisms through various signaling pathways etc
- Passage or transfer of information from primary cancer cells to the adjacent stromal cells.

Before the metastatic process the cancer cells not only self equip themselves with the above mentioned arrangement to enable their unhindered proliferation against the host or would be patient's immunological confrontations which may be lethal sometimes but inadequate. In some of the former may be plausible as in the case of immuno incompetent hosts. In the former cases only, the plethora of structural and functional categories of cancer becomes a realization event.

Once the cancers malignant properties have been accomplished in the absence of hosts immune surveillance and failure of the various host defense mechanisms the metastatic invasion begins, Involving the following major steps / stages viz.,

- Invasion or movement of cancer cells from their primary foci into the surrounding host tissue.
- Penetration of cells into the blood and/or lymph vessels:
- Shedding or release of tumour cell emboli either is individual cells or small clumps into the circulation (lymphatic/haematogenic)
- Passage of these emboli within the circulation
- Reaching by ORGANOTROPISM to alien tissue /organs and their / embedding into those distant organs and unique properties which enable the immune compromisation, seeding with specific or the secondary foci.

- Extraveasation of the cancer emboli into the secondary stroma and finally multiplication of these primary metastatic cells to establish the secondary population or the secondary metastatic nodule.

The different survival rate among patients diagnosed of cancer at the beginning stages (I&II) and the total failure of interventional therapies at later stage (III&IV) drive home the point that cancer growth and metastasis are determined by several probabilities and improbabilities. The probable factors would drive the cancer cells in their expedition from proliferation up to metastasis and settlement in distant organs and the accomplishment of a secondary population of cancer. On the contrary the improbable factors will act against these accomplishments of primary cancer cells. The availability of glucose metabolite inside a cancer patient is the first and formost probabilities factor, detrimental to cancer cell destruction and on the contrary it may augment the cell survival and its proliferation through mitogenesis.

- First and foremost role of glucose inside a cancer cell is the augmentation of anaerobic glycolysis or Warburg effect. Warburg[7].
- The resultant product of the above cancer cell glycolysis Viz., the lactic acid brings about the acidic pH which is congenial for the growth of cancer cells.
- Even in the absence of supply of glucose directly as an explicit metabolic substrate gluconeogenesis may be operated wherein the lactate may be converted to glucose to feed the cells as in cori cycle.

Glucose is also an inhibitor of anti microtubule drugs. In the case of microtubule inhibitor drugs like podophyllotoxin, glucose in cancer cells will enable the glycosylation of phyllotoxins and cause steric hindurance to the latter and its interference with the microtubular assembly.

PROBABILITY

COX-2 enzyme inside the cancer cells generate the prostaglandins-E (PGE_2) which can induce proliferation of cancer cells.PGE_2 may be mitogenic directly acting on cancer cells or contrarily it may act as a comitogenic factor alongside a cancer promoting agent. For instance 120-tetradecanyl-13 acetate (TPA) and its topical application on mouse skin was reported to induce PGE synthesis which in turn caused epidermal hyper proliferation Lee et al.[8]. In addition that already revealed that topical application of PGE in rat skin increased the synthesis of DNA, RNA and protein synthesis.

Further studies reported that Gatenby.R.A et al.[8] the growth stimulating effects of PGE seems to be linked to biological modifiers such as polyamines. The latter enhanced the activity of Ornithine decarboxylase (ODC) which in turn increased the DNA synthesis required for tumour proliferation and growth. Thus it is construed that the association between a cancer causing agent. 1. Prostaglandins (PGE) 2.Polyamines (PM) 3.ODC 4.Ornithine decarboxylase 5. DNA 6.Proteins are working in a continuum or in a dependent fashion of one on another to promote the proliferation and tumorigenesis

Several studies have also established that PGE_2 have a direct role rendering the cancer cells resistance capacity to apoptosis.

IMPROBABILITIES

The prostaglandins as mentioned per se represent an associating mitogen/ comitogen alongside a cancer causing agent. It is also referred to as endogenic biological modifiers in cells. Its involvement in the diverse biological functions of a cell is due to its manifolds actions. The PGEs-through specific G-Protein linked receptors modulate the levels of CAM_P and Ca++ Xie et al.[9], Simon et al.[10]. According to the view and opinion attributed by the PGE lipid molecules are not by themselves mitogenic in function they act as a permissive factor for the mitogenic action of several growth factors like epidermal growth factor (EGF) and insulin like growth factor (IGE)-I

In all cancer cells, the COX-2 over expression leads to the chain of events mentioned per se which render the cancer cells resistant to apoptosis. This has also been demonstrated in rat intestinal epithelial cells and in human prostate cancer cells transferred genetically. Liu et al.[11], PGE and their inhibitory anti-apoptotic effects in cancer has also been constructed to be accomplished by the inhibitory signals following uptake of PGE through the PGE transporter and / or due to its role as cAMP elevating agent.

In view of the above reports and findings it is tenable to conclude that genetic modulation by a risk factor or causative agent and the chain of events starting from glucose uptake, lactate synthesis, milieu alteration COX-2 ever expression, synthesis of PGE, synthesis of growth factors elevated polyamines, activation of ODC and synthesis of DNA are all coordinated and / or integrated to culminate the tumourigenesis. All the above mentioned the probability factors in cancer, (Fig) are exceptions to embryological rules.

CONCLUSION

Cancer cells undergoing the process of diseases manifestation and continuum reflect or document evidences for the various player molecules such as sugars, cholesterol, triglycerides lactic acid n-6 essential fatty acids,COX-2 over expression, PEG_2 synthesis, aromatase enzyme abnormal synthesis, growth factors etc., formed from within as well contributed from without. The given illustration below in Figure-1 revealed to above intricacies and metabolic exceptions that contribute the success of cancer cells and to the failure of drug mechanisms. However the cancer biology and its understanding of malignancy with resemblance to prokaryotic protein machinery prompts anti-cancers, therapy and its success towards drug designs against the prokaryotic homologs. Thus future cancer drugs ought to be based on evolutionary perspectives rather than by the disease perspectives.

References

[1] Ramalingam.K (2015). Epidemiological indices for breast cancer in south Indian population. *Global oncology & cancer Conference (AT USA).*

[2] Singh Pooja., Francis and Ramalingam.K (2010). Rele of ethnic variations in TNF-α and TNF-β polymorphism and risk of breast cancer in india, *Breast cancer Research and Treatment*.

[3] Chu K., Cheng C.J., Ye X., Lee Y.C., Zurita A.J., Chen D.T., et. al.:(2008). Cadherin-11 promotes the metastasis of prostate cancer cells to bone. *Mol Cancer Res*; 6: pp. 1259-1267.

[4] Gatenby R.A., Gillies R.J., Brown J.S.:(2010). Evolutionary dynamics of cancer prevention. *Nat Rev Cancer;* 10: pp. 526-527.

[5] Balinsky.B.I(1997). An introduction to embryology, Philadelpia, P.A, Saunders.

[6] Ramalingam .K and Indra.D.Ramamurthy(2005). Cytotoxic effect of achetinn(Lectin) from Achatina fulica against a human mammary carcinoma cell line (MCF) invitro cellular & Development Biology-Animal

[7] Lee A.H., Tannock I.F.(1998). Heterogeneity of intracellular pH and of mechanism that regulates intracellular pH in populations of cultured cells. Cancer Res; 58: pp. 1901-1908.

[8] Liu W, Laitinen S, Khan S, Vihinen M, Kowalski J, Yu G, Chen L, Ewing CM, Eisenberger MA, Carducci MA, et al. (2009). Copy number analysis indicates monoclonal origin of lethal metastatic prostate cancer. Nat Med 15: 559–565.

[9] Warburg O.(1956) On the origin of cancer cells. Science.123(3191):309–314.

[10] Gatenby .R.A., Gillies R.J., Brown J.S., (2010) Evolutionary dynamics of cancer prevention.Nat Rev Cancer; 10:pp.526-527.

[11] Xie GX, Palmer PP. (2007) How regulators of G protein signaling achieve selective regulation. J Mol Biol. ;366:349–365.

[12] Simon MI, Strathmann MP, Gautam N. (1991) Diversity of G proteins in signal transduction. Science 252:802–808.