Cancer Therapy & Oncology
International Journal
ISSN: 2473-554X

Juniper Publishers
key to the Researchers

Mini Review
Volume 30 Issue 2 - October 2025
DOI: 10.19080/CTOIJ.2025.30.556283

Cancer Ther Oncol Int J

Cancer: Intricacies, Improbabilities and Exceptions

K Ramalingam[1]*, Babu K[2] and S Palraj[3]

[1]*Mediclone Biotech Research Centre, Chennai-48, Tamil Nadu, India & Chennai, Tamil Nadu, India*

[2]*Arignar Anna Government Arts College, Namakkal-637002, Tamil Nadu, India*

[3]*Executive Director, Snake Park Trust, Chennai*

Submission: September 17, 2025; **Published:** October 09, 2025

Corresponding author: K Ramalingam, Rai Memorial Medical (Cancer Hospital) Centre, (Ethical Committee), Chennai-48, Tamil Nadu, India

Abstract

Cancer is a multifactorial disease arising from complex interactions between genetic, epigenetic, and environmental factors, leading to aberrant cellular behavior that deviates from normal developmental cues. It is a multifaceted disease characterized by its defiance of normal developmental and metabolic rules, earning it the title "Emperor of Maladies." This article explores the intricate mechanisms underlying cancer initiation, progression, and metastasis, emphasizing the exceptions cancer cells present compared to normal cells. It discusses how genetic instability, mitochondrial mutations, and epigenetic alterations drive uncontrolled proliferation, while highlighting the unique role of cancer stem cells (CSCs) in tumor recurrence, therapeutic resistance, and metastasis.

Metabolic reprogramming, particularly the shift toward aerobic and anaerobic glycolysis (Warburg effect), is analyzed as a hallmark of cancer metabolism supporting rapid cell growth. Structural and functional changes at the membrane, cytoplasmic, organelle, and molecular levels contribute to cancer cells' survival, immune evasion, and invasive capabilities. The article also examines the probabilistic and improbable roles of prostaglandin E2 (PGE2), COX-2 overexpression, and polyamines in promoting or modulating tumorigenesis. It concludes that cancer progression represents a paradigm of exceptions to normal embryological development, driven by genetic and biochemical deviations. Understanding these intricacies is crucial for designing targeted therapies and improving prognostic strategies in oncology, as conventional treatments often fail against the resilient and adaptive nature of cancer cells.

Keywords: Tumorigenesis; Metastasis, Cancer Stem Cells; Apoptosis Evasion; Prostaglandin E2 (PGE2); Ornithine Decarboxylase (ODC)

Abbreviations: EGF: Epidermal Growth Factor; CSCs: Cancer Stem Cells; PG E2: Prostaglandin E2; SNPs: Single Nucleotide Variations; ODC: Ornithine Decarboxylase

Introduction

Cancer is a disease of multiple etiologies induced by innumerable intrinsic and extrinsic risk factors (prognostic) which deviate a normal tissue or cell from general developmental cues and paradigms [1]. A perusal of literature on the biology of cancer cells reveals that a cancer cell, consequent to the chronic induction of etiological factors and the concurrent accumulation of mutations in both the nuclear and mitochondrial genome [2], undergoes a process of disease manifestation due to chronic and persistent stimuli and the cumulative responses by the cell.

It also involves a series of biochemical reactions occurring in different phases due to both the expression and suppression of genes of the reparable nuclear genome and the irreparable mitochondrial genome, and their epigenetic expression 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 hundred thousand mutations [3] or single nucleotide variations (SNPs). The enormous changes that are discernible in the normal genome sequences make the disease cancer unique and confer it the title of the "EMPEROR OF ALL MALADIES" in humans.

Even gene therapy has not been able to cure the disease in modern therapeutic strategies, since cancer is not monogenic but multigenic. The development of cancer, or the transformation of a normal cell into a cancer cell, takes on different profiles: initiation, transformation, proliferation, growth, invasion/metastasis, secondary development, and death. This represents a continuum inside the body of a patient, taking a long latent period of 15–20

years, challenging every formidable reaction of the individual and overcoming all immunological surveillance and responses of the host. Understanding the various intricacies of cancer disease reveals that cancer cells deviate from the normal features of cells.

In a normal individual, growth occurs due to the culmination of various physiological, biochemical, and metabolic reactions, coordinated with other profiles of endocrine [4] and immunological organs, abiding by all the rules of the developmental process with few or far exceptions. On the contrary, the development of cancer takes on an entirely different profile where exceptions are the established rules.

In normal embryological development and growth, cells know by virtue of their positions what to do and differentiate as per a pre-determined pattern and sequence. The functions of homeotic genes in development are evidence of this [5]. Similarly, the concept of primary and secondary organizers (Spemann and Mangold) is evidence for the sequential development of organs. But in cancer development, the cells follow abnormal commands executed by genomic alterations and proceed in a neoplastic pattern where there are no rules, but only exceptions prevail.

Cancer Stem Cells: A Deviation and an Exception

The earlier description of cancer stem cells was as several fully viable proliferating clonogenic cancer cells [6]. However, later studies have revealed that in a tumor mass, about 0.8–1% of cells-which are both chemo-resistant and radiation-resistant-are stem cells. The similarity between normal tissue stem cells and cancer stem cells is that in the former, stem cells proliferate to reinstate normal cells after tissue injury, while in the latter, stem cells repopulate the resistant cancer cells even after surgery, chemotherapy, and radiation therapy. In a mass of malignant tissue, cells nearest the blood supply, well-oxygenated and well-nourished, are most likely to survive and proliferate.

These are killed by cytotoxic chemotherapeutic drugs. However, some hypoxic cells acquire new immunological competence and survive as stem cells. These cancer stem cells express novel surface antigens different from other cancer cells and become resistant to drugs and radiation, protected against free radicals, equipped with anti-apoptotic proteins, and capable of reviving cancer in distant organs via metastasis.

They remain a challenge to current therapeutic strategies in clinical settings to this hour. Besides the above-mentioned cancer stem cells, resistant cancer cells also contribute to the 10-30% of cancer recurrence in patients after treatment. Such recurrence was noticed both at the primary site and in nearby lymph nodes and tissues, as well as in distant organs. These 10-30% of patients possess a multi-drug resistance gene (mdr1), which is over-expressed to produce high levels of glycoproteins, viz., P-gp that act as proton pumps to expel cytotoxic drugs from cancer cells and enable their survival [1].

Metabolic Exceptions

Among the biochemical constituents, refined sugar in cancer patients provides the fuel for the cancer cells' anaerobic glycolysis mechanism selectively. A Russian scientist, Vladimir M. Dilman, has adduced evidence for the link between sugar/carbohydrate and cancer etiology [7]. 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 the anaerobic side, all cancer patients may have high insulin and triglycerides to promote the Warburg effect in their cancer cells, enabling them to subsist on minimal energetic metabolism, which could have been mediated through a genetic switch-on mechanism.

This is again evidence of 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 progenitor prokaryotic cells which respired anaerobically and subsisted in the reducing atmosphere of the Archeozoic/Proterozoic era. Such genetic modulation in a cancer cell may be an exception to their normal counterparts in the same patient's body or in normal individuals. The above evolutionary shift in oxidative energy metabolism and the reversal of the 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 established cues and rules in cellular metabolism. Cancer cells no doubt employ diverse mechanisms to promote their own growth and proliferation, and these mechanisms continue to operate until the cells arrive at the stage to undertake the deleterious invasion of distant organs through metastasis. The growth process and stepwise changes that take place inside a cancer cell journey in a continuum, a chunk of yet-to-be-fully-analyzed understanding at the forefront of cancer biology.

Structural and Functional Changes in Cancer Cells

All cancer tumors may begin in nature at the beginning of differentiation, showing typical normal cellular characteristics in their structures and such functional attributes as slow growth, low mitotic rate, and index. This contrasts with malignant neoplasms, which have acquired rapid growth potential, a high mitotic index, and consist of undifferentiated anaplastic cells. The transition between a passive phase to the malignant state involves a plethora of both structural and functional aspects which include, in broad categories:

Cancer cells undergo:

- Membrane-level changes in lipid composition.

How to cite this article: K Ramalingam, Babu K. Cancer: Intricacies, Improbabilities and Exceptions. Canc Therapy & Oncol Int J. 2024; 30(2): 556283. DOI: 10.19080/CTOIJ.2024.30.556283

- Cytoplasmic changes involving specific receptors, messengers, and molecular chaperones.
- Organelle-level alterations in their basic sequences of nucleotides.
- Changes in enzyme components to boost the metabolic profiles of cancer cells.
- Epigenetic expression of proteins both in the intra- and extracellular milieu and, lastly, anti-apoptotic mechanisms through signaling pathways.
- Transfer of information from primary cancer cells to adjacent stromal cells.
- These enable their survival and proliferation, overcoming host immune responses, and eventually allowing invasion and metastasis.

Metastasis Road Map

Before the metastatic process, cancer cells not only self-equip themselves with the above-mentioned arrangements to enable their unhindered proliferation but also prepare against the host's (the would-be patient's) immunological confrontations, which may sometimes be lethal but are often inadequate. The former scenario may be plausible in the case of an immune-incompetent host, while the latter may occur in immuno-competent hosts. Once the cancer's malignant properties have been accomplished in the absence of host immune surveillance and due to the failure of various host defense mechanisms, the metastatic invasion begins, involving the following major steps or stages:

1. Invasion of surrounding tissues from the primary site.
2. Penetration into blood and/or lymph vessels.
3. Circulation through bloodstream or lymphatics.
4. Escape from immune surveillance.
5. Establishment in secondary sites.
6. Proliferation and formation of secondary tumours.
7. Shedding or release of tumor cell emboli, either individually or in small clumps, into circulation (lymphatic or hematogenous).
8. Passage of these emboli within the circulation.
9. Arrival at alien tissues/organs and embedding into those distant organs, enabled by unique properties which allow immune evasion and seeding to form specific or secondary foci.
10. Extravasation of the cancer emboli into the secondary stroma and finally, multiplication of these metastatic cells to establish a secondary population or a secondary metastatic nodule.

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

The first and foremost role of glucose inside a cancer cell is the augmentation of anaerobic glycolysis or the Warburg effect [8]. The resulting product of the above cancer cell glycolysis, viz., lactic acid, brings about an acidic pH which is congenial for the growth of cancer cells. Even in the absence of a direct supply of glucose as an explicit metabolic substrate, gluconeogenesis may be operated wherein lactate may be converted to glucose to feed the cells. 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 hindrance to the latter, interfering with microtubular assembly.

Probabilities

The COX-2 enzyme inside cancer cells generates prostaglandin E2 (PGE2), which can induce the proliferation of cancer cells. PGE2 may be mitogenic, acting directly on cancer cells, or it may act as a co-mitogenic factor alongside cancer-promoting agents. For instance, 12-O-tetradecanoylphorbol-13-acetate (TPA) and its topical application on mouse skin was reported to induce prostaglandin synthesis, which in turn caused epidermal hyperproliferation [9].

In addition, Lupulescu (1977) [10] revealed that topical application of PGE in rat skin increased the synthesis of DNA, RNA, and protein [10]. Further studies reported that the growth-stimulating effects of PGE seem to be linked to biological modifiers such as polyamines [11]. The latter enhanced the activity of ornithine decarboxylase (ODC), which in turn increased the DNA synthesis required for tumor proliferation and growth. Thus, it is construed that an association between the cancer-causing agent,

1. Prostaglandin (PGE),
2. Polyamines (PM),
3. ODC,
4. Ornithine decarboxylase,
5. DNA, and
6. protein is working in a continuum or in an interdependent fashion to promote proliferation and tumorigenesis. Several

How to cite this article: K Ramalingam, Babu K. Cancer: Intricacies, Improbabilities and Exceptions. Canc Therapy & Oncol Int J. 2024; 30(2): 556283. DOI: 10.19080/CTOIJ.2024.30.556283

studies have also established that PGE2 has a direct role in rendering cancer cells resistant to apoptosis [12].

Improbabilities

The prostaglandins, as mentioned per se, represent an associating mitogen/co-mitogen alongside a cancer-causing agent. They are also referred to as endogenous biological modifiers in the milieu of cells. Their involvement in the diverse biological functions of a cell is due to their manifold actions. PGEs modulate the levels of cAMP and Ca++ through specific G-protein-linked receptors [13,14]. According to the view attributed to Pentland and Needleman (1986) and Nolan et al. (1988) [15,16], 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 (IGF)-1 [15,16].

In all cancer cells, COX-2 overexpression 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 genetically modified human prostate cancer cells [17,18]. The inhibitory anti-apoptotic effects of PGEs in cancer have also been construed to be accomplished by inhibitory signals following the uptake of PGE through the PGE transporter and/or due to its role as a cAMP-elevating agent [19].

Conclusion

In view of the above reports and findings, it is tenable to conclude that genetic modulations by a risk factor or causative agent and the chain of events-starting from glucose uptake, lactate synthesis, milieu alteration, COX-2 overexpression, synthesis of PGE, synthesis of growth factors, elevated polyamines, activation of ODC, and synthesis of DNA-all integrate to culminate in tumorigenesis. These probability factors represent clear exceptions to the rules of embryological development.

References

1. Ramalingam S (2017) Prudent proxies to prevent cancer (Personal Publication) p: 160.
2. Francis FZ, Anandharaj A (2004) Mitochondrial genome instability in cancer. Journal of Molecular Biology 335(2): 345-356.
3. Perucho M, et al. (2011) The mutational landscape of cancer. Nature Reviews Cancer 11(12): 835-848.
4. Norman AW, Litwack G (1987) Hormones. Academic Press, USA.
5. Balinsky BI (1981) An Introduction to Embryology. Saunders College Pub.
6. Brachet J, Mirsky AE (1961) The Cell: Biochemistry, Physiology, Morphology. Academic Press, USA.
7. Dilman VM (1971) The Law of Deviation of Homeostasis and Diseases of Aging. John Wright PSG.
8. Warburg O (1956) On the origin of cancer cells. Science 123(3191): 309-314.
9. Haniffa M, et al. (1996) Phorbol ester-induced prostaglandin synthesis and epidermal hyperproliferation. Carcinogenesis 17(5): 1021-1026.
10. Lupulescu A (1977) Prostaglandins and their role in protein synthesis. Journal of Investigative Dermatology 68(5): 277-280.
11. Craven PA, et al. (1993) Polyamines and ornithine decarboxylase in tumor promotion. Cancer Research 53(15): 3541-3546.
12. Tsujii M, DuBois RN (1995) Alterations in cellular adhesion and apoptosis in epithelial cells overexpressing prostaglandin endoperoxide synthase 2. Cell 83(3): 493-501.
13. Xie W, et al. (1992) Expression of a mitogen-responsive gene encoding prostaglandin synthase is regulated by mRNA splicing. Proceedings of the National Academy of Sciences 89(12): 5326-5330.
14. Simmons DL, et al. (1991) Induction of prostaglandin H synthase by phorbol esters in human promyelocytic leukemia cells. Journal of Biological Chemistry 266(22): 14548-14553.
15. Pentland AP, Needleman P (1986) Modulation of keratinocyte proliferation in vitro by endogenous prostaglandin synthesis. Journal of Clinical Investigation 77(1): 246-251.
16. Nolan RD, et al. (1988) Eicosanoid synthesis in 3T3 fibroblasts: mitogenic stimulation by epidermal growth factor. Biochemica et Biophysica Acta (BBA) - Lipids and Lipid Metabolism 959(1): 46-57.
17. Liu XH, et al. (1998) Overexpression of cyclooxygenase-2 is sufficient to induce tumorigenesis in transgenic mice. Journal of Biological Chemistry 273(34): 22120-22127.
18. Kawamura T, et al. (1999) Prostaglandin E2 promotes survival of naive U937 cells via cAMP-mediated inhibition of spontaneous apoptosis. Cancer Research 59(16): 3915-3921.
19. L Ottonello, R Gonella, P Dapino, C Sacchetti, F Dallegri (1998) Prostaglandin E2 inhibits apoptosis in human neutrophilic granulocytes via EP2 and EP4 receptors. American Journal of Physiology-Cell Physiology 275(6): C1555-C1561.

How to cite this article: K Ramalingam, Babu K. Cancer: Intricacies, Improbabilities and Exceptions. Canc Therapy & Oncol Int J. 2024; 30(2): 556283. DOI: 10.19080/CTOIJ.2024.30.556283

DOI: 10.19080/CTOIJ.2024.30.556283

How to cite this article: K Ramalingam, Babu K. Cancer: Intricacies, Improbabilities and Exceptions. Canc Therapy & Oncol Int J. 2024; 30(2): 556283. DOI: 10.19080/CTOIJ.2024.30.556283