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MYSTERY OF MALIGNANT CELLS

Raghavendra Rao M V*	Professor of Microbiology and Vice-President of the World Academy of Medical Sciences, Netherlands (Europe) *Corresponding Author
Chinnababu Sunkavalli	Clinical Director & Consultant Surgical Oncologist, Yashoda Hi-tec City Hospital, Hyderabad, India
Daniel Finney Sankuru	Postgraduate, Department of Community Medicine, Katuri Medical College & Hospital, Guntur, India
Prisha Susanne Sunkavalli	First year MBBS student, Apollo institute of medical sciences and research, Hyderabad, TS, India.
Priyanka Sunkara	second-year pre-medical biochemistry student at the New Jersey Institute of Technology in New Jersey, USA
Sumedha Sahanasree	Consultant Dentist, Andhra Prime Hospitals, Guntur, India
M M Karindas	Professor of Oncology, and President World Academy of Medical Sciences, Netherlands (Europe)

ABSTRACT

Cancer is the second most common cause of death in the United States and accounts for nearly one in every four deaths. Generally, normal cells grow and multiply through controlled cell division, where old and damaged cells are replaced by new cells after they die. Cancer represents an excessive division of cells. The cancer cell cycle involves dysregulated cell proliferation due to defects in the normal, regulated process of cell division. Key factors include mutations in oncogenes and tumour suppressor genes, leading to unchecked growth signals and loss of control at cell cycle checkpoints. This results in cancer cells dividing uncontrollably, forming tumours, and exhibiting abnormal growth, invasion, and metastasis. Genomic instability and mutations underlie the hallmarks of cancer. Mutations can transform normal cells into cancerous ones by endowing them with new properties. Cancer metastasis is the major cause of cancer-associated death. These biomarkers are often used for screening, detection, diagnosis, prognosis, prediction, and monitoring of cancer development. Studies have shown that tumour cells may have an increased level of surface phosphatidylserine. Calreticulin is expressed on the cell surface. Normally, calreticulin is located in the endoplasmic/sarcoplasmic reticulum, in the cell nucleus, and partly on the surface membrane. Cellular stress induces its surface expression. Certain cancers present super-expression of surface calreticulin, but most normal cells have low calreticulin levels

INTRODUCTION

During interphase, some subdivisions are important to cell division and the maintenance of the genetic material. The subdivisions consist of G1, S, and G2. (1)

After mitosis, where the cells divide into 2 cells, they enter the G1 phase, which is a place for resting and a checkpoint for complete genetic function before the cells can start replicating the DNA. (2)

The cells never die in cancer, as cancer cells can utilize telomerase to add many telomeric sections to the ends of DNA during DNA replication, allowing the cells to live much longer than other somatic cells. (3)
The tumour suppressor gene plays a crucial role in maintaining the cell cycle is p53, which is a transcription factor that plays a role in promoting growth arrest, DNA repair, and eventual apoptosis, by the cell in damaging situations. (4)

One of the major DNA repair mechanisms is called Base excision repair, which is responsible for repairing mismatched bases throughout the entire cell cycle. Additionally, p53 also regulates the expression of many inhibitory proteins, like p21, GADD45. (5)

Cancer may also develop during the S phase if repair mechanisms like the ones discussed previously are not functional or if DNA polymerase loses its function to proofread mismatched pairs during the S phase, leading to unstable DNA and possible frameshift mutations that result in nonfunctional regulator proteins. (6)

Many chemotherapy drugs work to break strands of DNA to stop the replication of the cells once suppression has been bypassed; however. (7)

Poor response to therapies due to the development of resistance in tumors remains a significant clinical challenge and contributes to the overall poor patient prognosis. (8)

While still being utilized for the treatment of locally advanced or metastatic pancreatic cancer, the effectiveness of gemcitabine has been constrained by the frequent development of resistance to this drug in most of the treated patients (9)

Recently, FOLFIRINOX (fluorouracil, leucovorin, irinotecan, and oxaliplatin) has been approved as a treatment for patients with advanced pancreatic ductal adenocarcinoma, showing significantly improved overall and median progression-free survival compared with gemcitabine, albeit with a less favourable toxicity profile (10)

The Hallmarks of Cancer were proposed as a set of functional capabilities acquired by human cells as they make their way from normalcy to neoplastic growth states, more specifically, capabilities that are crucial for their ability to form malignant tumours. (11)

The acquired capabilities for sustaining proliferative signalling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing/accessing vasculature, activating invasion and metastasis, reprogramming cellular metabolism, and avoiding immune destruction.(12)

Metastasis, a process during which cancer cells dissociate from a primary tumor to navigate through interstitial tissues and ultimately colonize distant organs, is responsible for about 90% of cancer-associated deaths (13)

To establish metastatic foci, cancer cells of solid tumours disseminate from the primary tumour site, intravasate into blood or lymphatic vessels, circulate through the body, extravasate to distant sites, and proliferate to form secondary tumours (14)

Exosomes are small extracellular vesicles that are secreted from late endosomal multivesicular endosomes.(15)

However, recent reports indicate that exosomes are secreted from virtually all cell types, including normal and cancer cells, and play an important role in autocrine and paracrine communication.(16)

The mechanical properties of living cells, including their shape, rigidity, and internal dynamics, play a crucial role in cell physiology and pathology (17)

The mechanical response of the cell generally depends on its three main mechanical components: the cytoskeleton, the nucleus, and the cytoplasm. (18)

NK cells are defined as CD56+; CD3- and can be overall classified into two distinct subsets: CD56bright CD16- and CD56dim CD16+. (19)

The first subset is thought to be a not fully mature group of NK cells, which account for 5-10% of peripheral blood NK cells and can secrete large amounts of cytokines (20)

DNA- A New Twist On Life

The discovery in 1953 of the double helix, the twisted-ladder structure of deoxyribonucleic acid (DNA), by James Watson and Francis Crick marked a milestone in the history of science and gave rise to modern molecular biology, which is largely concerned with understanding how genes control the chemical processes within cells.

Characteristics of a Normal Cell--

Growth is slow. Structure is typical. Mitosis cell division is typical.

Characteristics Of A Malignant Cell-

Growth is rapid. Structure is Atypical. Mitosis cell division is Atypical. Cell destruction and Necrosis are common. The malignant cell is characterized by acceleration of the cell cycle; genomic alterations; invasive growth; increased cell mobility; chemotaxis; changes in the cellular surface; secretion of lytic factors, etc.

Cancer And Cell Cycle

Cancer represents an excessive division of cells. In cancer large quantity of cells are in mitosis, and most of them S-phase. The majority of drugs used for cancer therapy are designed to block DNA replication or inhibit the enzymes that participate in replication. Methotrexate (inhibits dihydrofolate reductase) and 5-fluorouracil (inhibits thymidylate synthase) block nucleotide synthesis. In recent years, topoisomerase inhibitors have been used. They block the unwinding of parental DNA strands and prevent replication.

Key factors include mutations in oncogenes and tumour suppressor genes, leading to unchecked growth signals and loss of control at cell cycle checkpoints. This results in cancer cells ls dividing uncontrollably, forming tumours, and exhibiting abnormal growth, invasion, and metastasis.

Genomic And Epigenomic Alterations In Cancer

Numerous studies revealed a myriad of acquired alterations in cancer. The alternations/mutations are heterogeneous and found among different tumours. Some of the more common genomic alterations include copy number variations, including amplification or deletion of genomic regions. (21)

Chromosomal rearrangement and gene fusions are another common class of genomic aberrations in cancer. After the discovery of the Philadelphia chromosome in 1960 as a specific chromosome change in chronic myeloid leukemia, multiple studies have shown the occurrence of fusion genes in a variety of cancers and through many different approaches (22)

The landmark discovery of *BCR-ABL1* kinase fusion led to the discovery of the small-molecule inhibitor imatinib (Gleevec) for targeting patients with this fusion gene. Gene fusions were commonly discovered in hepatological malignancies. (23)

These common gene fusions in prostate cancer involve the transmembrane protease serine 2 gene (*TMPRSS2*) with two genes encoding ETS transcription factors, either v-ets avian erythroblastosis virus E26 oncogene homologue (*ERG*; resulting in the *TMPRSS2-ERG* fusion gene) or variant 1 (ETV1; resulting in the *TMPRSS2-ETV1* fusion gene) (24)

Malignant Cell And Invasive Growth

A malignant tumour is characterized by the possibility to implement such a biological phenomenon as the metastatic cascade, that is, a unique multi-stage "program" where cell invasion is a trigger and a key factor for further cancer progression and metastasis in distant organs and tissues. (25,26)

The range between "end" points of a complex invasive metastatic process –invasion of the primary tumour into surrounding tissues and the formation of metastatic foci –comprises several stages, the passage of which is strictly necessary for the successful development (27,28).

The factors limiting the growth of malignant neoplasms include the basal membrane and various components of the surrounding stroma, increased interstitial pressure, limited oxygen supply to tumour cells, and the formation of active oxygen forms, hypoxic conditions, and permanent exposure to immune system cells. (29)

Invasive tumour growth is enabled by the detachment of malignant cells from the tumour mass due to a reduction in or complete loss of intercellular adhesion molecules, and, therefore, the cells gain the ability of anomalously high motility, enabling penetration through the stiff structural elements of the surrounding stroma (30).

The invasion process extensively involves various molecular and cellular mechanisms that, according to published data, depend directly on another biological phenomenon – the epithelial-mesenchymal transformation, which was first described by E.D. Hay in 1995 (31)

Currently, EMT is known to underlie the processes of embryogenesis and inflammation and regeneration of tissues and, certainly, plays a key role in the mechanisms of carcinogenesis (32)

Cancer Cell Metastasis

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Certain phenotypes are required to overcome the physical barriers presented to cancer cells during metastasis. For example, intravasation and extravasation require cells to deform considerably to pass through the narrow interstitial space in the endothelium and epithelium of the vessel wall (35).

In addition to cell mobility, deformability is equally critical for cancer cells to navigate the confined space in the tissues during metastasis (36).

Cellular deformability correlates with the viscoelasticity of the cell, which could be probed by atomic force microscopy (AFM), micropipette aspiration, and magnetic tweezers (37)

Cancer cell-Chemotaxis

Cell migration is an essential component of metastatic dissemination of tumour cells from the primary tumour to local and distant sites (38,39)

Although tumour cells can move both randomly and directionally, invasion, migration, and dissemination are most efficient when the cell is involved in directed migration. (40) Different types of directed cell migration have been observed in tumour cells: chemotaxis, hypotaxis, electro taxis, and Duro taxis (41)

The location and type of cue theoretically determine which of these types of directed cell migration is engaged. Directed migration towards a soluble chemotactic agent is traditionally called chemotaxis, migration towards a substrate-bound agent is called hypotaxis (42)

Although the shape and amplitude of a soluble chemotactic gradient delivered experimentally *in vitro* can be defined with precision, current technology does not allow the distinction of chemotaxis *in vivo* towards soluble factors from chemotaxis towards factors partially or fully bound to the ECM and/or cell surfaces. (43,44)

For example, *in vitro* binding studies indicate that cytokines can become immobilized to form solid-state gradients, which suggests that both soluble and solid-state gradients might contribute to chemotaxis *in vivo (45)*

Chemotaxis is the result of three separate steps: chemo sensing, polarization, and locomotion (46)

Release Of Intracellular Contents

Tumor lysis syndrome arises from the rapid breakdown of tumor cells, leading to significant metabolic disturbances such as hyperkalemia, hyperphosphatemia, hypocalcemia, and hyperuricemia. These disturbances can result in severe complications, including acute kidney injury, cardiac arrhythmias, and even death.

Patients at high risk of developing tumour lysis syndrome typically have neoplasms with a high proliferative rate and significant sensitivity to chemotherapy. Prevention and early intervention are crucial. Strategies include aggressive hydration; the use of hypouricemic agents, such as allopurinol or rasburicase; and close monitoring of metabolic parameters.

Cancer-changes In The Cell Surface

Crucial cell functions, including migration, cytokinesis, and differentiation, involve major changes in cell shape. Morphological transformations often result in dramatically different cell shapes, requiring cells to develop efficient mechanisms to manipulate surface area while keeping volume nearly constant. (47)

The periphery of the cell, which we term the cell surface, must be very flexible to accommodate fast shape changes during migration while maintaining the integrity of the cell. (48)

These surface projections largely disappear upon cell spreading, leading to the hypothesis that they serve as a reservoir for storing the excess of the PM that can be flattened and reused during surface expansion (49)

Cancer Cell Secretion Of Lytic Factors

Tumour lysis syndrome is a critical medical condition that arises from the rapid breakdown of tumour cells, leading to significant metabolic disturbances such as hyperkalaemia, hyperphosphatemia, hypocalcaemia, and hyperuricemia. These disturbances can result in severe complications, including acute kidney injury, cardiac arrhythmias, and even death. Tumor lysis syndrome is commonly observed in patients undergoing treatment for hematologic malignancies such as non-Hodgkin lymphomas, acute leukemias, and Burkitt lymphoma, particularly following the initiation of chemotherapy. However, tumour lysis syndrome may also occur spontaneously. Patients at high risk of developing tumour lysis syndrome typically have neoplasms with a high proliferative rate and significant sensitivity to chemotherapy. Prevention and early intervention are crucial. Strategies include aggressive hydration; the use of hypouricemic agents, such as allopurinol or rasburicase; and close monitoring of metabolic parameters. (50)

How To Navigate Uncertainty In Cancer Patients

People with cancer experience a considerable amount of uncertainty and emotional distress during and post-treatment. (51)

If not properly managed, this distress leads to treatment burden, such as poorer functioning and well-being associated with treatment and self-care activities; poorer symptom management; and poorer health-related quality of life (52)

The COVID-19 pandemic adds additional psychological burden as cancer patients worry about the risk of COVID-19 infection and serious disease, social isolation, loss of social support, along with delays, disruptions, and postponement of needed procedures and treatment (53)

To maintain continuity of care, a large proportion of cancer care services have transitioned from in-person to telehealth (54)

How Do Cancer Cells Survive Chemotherapy?

To start with, some cancers are intrinsically resistant to anticancer drugs (55)

Furthermore, apoptosis avoidance, mitogenic self-sufficiency, and insensitivity to anti-proliferative stimuli are hallmarks of cancer. Killing sensitive cancer cells, an initially effective cancer therapy, inevitably selects for acquired resistance. Resistant clones tend to be aggressive due to acquiring additional oncogenic mutations. (56)

Malignant Cell And Immunotherapy

Immunotherapy works differently from traditional treatments like chemotherapy and radiation. Instead of attacking all rapidly dividing cells, it strengthens the immune system's natural ability to identify and eliminate cancer cells specifically.

Cancer:The Queen of All Maladies

Cancer begins and ends with people. In 2010, about six hundred thousand Americans and more than 7 million people around the world will die of cancer. In the United States, one in three women and one in two men will develop cancer during their lifetime. A quarter of all American deaths, and about 15 percent of all deaths worldwide, will be attributed to cancer. In some nations, cancer will surpass heart disease to become the most common cause of death.

How A Nano Knife Can Find And Kill The Smallest Of Cancer Cells?

The needles are placed in or around a tumour. And then you have to pass very high voltage electricity between any two needles at a time.This process punctures very small holes into the cell membranes, which result in cell death,' says Dr Sanjay Saran Baijal, Chairman, Diagnostic and Interventional Radiology, Medanta, Gurugram.

When 57-year-old Kishan, a patient suffering from non-alcoholic steatohepatitis — liver inflammation resulting from an excessive fat accumulation in the organ — was getting a routine CT scan done, he had not bargained for cancer. During the process, doctors at Medanta, Gurugram, detected a lesion in his kidneys, which turned out to be a malignant tumour.

This came as a shock to Kishan, as before the CT scan, he did not have any symptoms of cancer. Initially, the doctors adopted a multi-disciplinary approach. Since it was a renal cancer, the urologist became the mainstay of the treatment strategy. The team consisted of the urologist, the liver specialists who were managing his other co-morbidities, and the diagnostic and interventional radiology team. (57)

Why Do Sleeping Cancer Cells Awaken?

Dormant cells often are those that have broken away from the primary tumour and travelled to distant parts of the body. When they awaken, they create metastatic tumours that may be more difficult to treat than the original cancer. In an analysis published in April 2020 in the Experimental & Molecular Medicine journal, researchers at South Korea's Gwangju Institute of Science and Technology describe awakened cancer cells as "the final step of the metastatic outbreak." Metastasis accounts for 90 percent of all cancer deaths.

Research on Dormant Cancer Cells Aims to Prevent Metastasis

Cancer cells that spread to other parts of the body early in the disease and then enter a sleeping, or dormant, state, according to a growing body of research.

These dormant cancer cells can survive in the body undetected for months, years, or even decades, the research suggests. At some point, however, the cells may awaken and begin the process of forming metastatic tumours.

In one study, dormant breast cancer cells that had migrated to the lungs were kept in check by immune cells that reside there, researchers at the Albert Einstein College of Medicine reported. (58)

CONCLUSION

In normal cell growth is slow, structure is typical. Mitosis cell division is typical. Whereas a malignant cell the growth is rapid. Structure and Mitosis are Atypical. Cell destruction and Necrosis are common. The malignant cell is characterized by acceleration of the cell cycle; genomic alterations; invasive growth; increased cell mobility; chemotaxis; changes in the cellular surface; secretion of lytic factors, etc. Tumour cells may have an increased level of surface phosphatidylserine. Normally, calreticulin is located in the endoplasmic/ sarcoplasmic reticulum, in the cell nucleus, and partly on the surface membrane.Normal cells with a low level of surface calreticulin are not destroyed because they send anti-phagocytic signals with their surface CD47. Certain cancers present super-expression of surface calreticulin, but most normal cells have low calreticulin levels. Enhanced CD47 expression correlates with high calreticulin expression, which is necessary to avoid calreticulin-mediated phagocytosis. The oxidative stress causes exposure of PS on the surface of the vascular endothelium in the cancer cells (lung, breast, pancreatic, bladder, skin, brain metastasis, rectal adenocarcinoma, etc.) but not on the normal cells.

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