Primordial Origin of Cancer

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Abstract

Oncological disorders are the second leading cause of death worldwide and now it has become a major threat in public health worldwide. We must understand behavior of cancer from evolutionary aspects to prevent, manage and treat this disease in a right way. This review, hypothesize the evolution and origin of cancer from unicellular organisms from different mechanisms, and microbiome interact with cancer cells in tumor microenvironment to protect and support each other and this plays important role in cancer formation and development. Also, the importance of healthy lifestyle and diet can prevent from causing cancer in later life is also discussed.

Keywords

Cancer, microbiome, unicellular organisms, tumor microenvironment, evolution, lifestyle and diet.

Introduction

Cancer is a disease as old as humankind. It has most likely been nearby since the multicellular organisms came into existence.[1]Besides, some Dinosaurs of the Jurassic period equally suffered from cancer.[3] However, the fundamental queries such as, what exactly is cancer and why does it exist, are currently unclear and unanswered. Despite of significant advances in our practical understanding of the disease, the origin of cancer remains a mystery.

Cancer is a multifactorial disease; nowadays, bad dietary habits, sedentary lifestyle, lack of sleep, environmental pollution, and temperature changes have undoubtedly become the crucial reasons for causing microbiota dysbiosis. Even a healthy diet plays a vital role here, nowadays, people are moving away from the traditional dietary pattern, which influences the risk of cancer. Recent studies showed that intake of a proper traditional diet, such as seasonal fruits, raw vegetables, legumes, probiotics, and good carbs has increased the beneficial and protective effects.[6] Therefore, avoiding cigarettes smoking, limiting alcohol consumption, maintaining normal BMI, regular exercise and proper sleep are effective steps for not only preventing cancer but also for other lifestyle diseases and disorders.

Cancer typically undergoes various complex biological processes and consists of a complex biological network, and it is hypothesizing through the process of positive and negative natural selection, which has been described by Charles Robert Darwin.[4] Natural selection theory suggest a mechanism of evolution. Organisms that are adapted to their environment are more likely to survive. This causes species to change and diverge over time. Positive and negative natural selection are types of natural selections, positive selection means variation or change that causes positive impact on the population, whereas negative selection means the variation or change cause deleterious impact on the population. During the evolution of multicellular life, it has presented major alterations in genetic and cellular phenotypes also observed in cancer,[1] but why such specific alterations naturally take place in cancer is still unknown. To perceive the accurate behavior of cancer, we must understand it through evolutionary theory, and this would provide perspective to develop a novel system and strategy to fight against cancer. Interestingly, there are various theories suggesting cancer formation is associated with the microbes which reside in the human body. However, these microbes play a vital role in the metabolism of nutrients, but changes in the microenvironment of the body engage in them to evolve and influence cancer formation.[5]

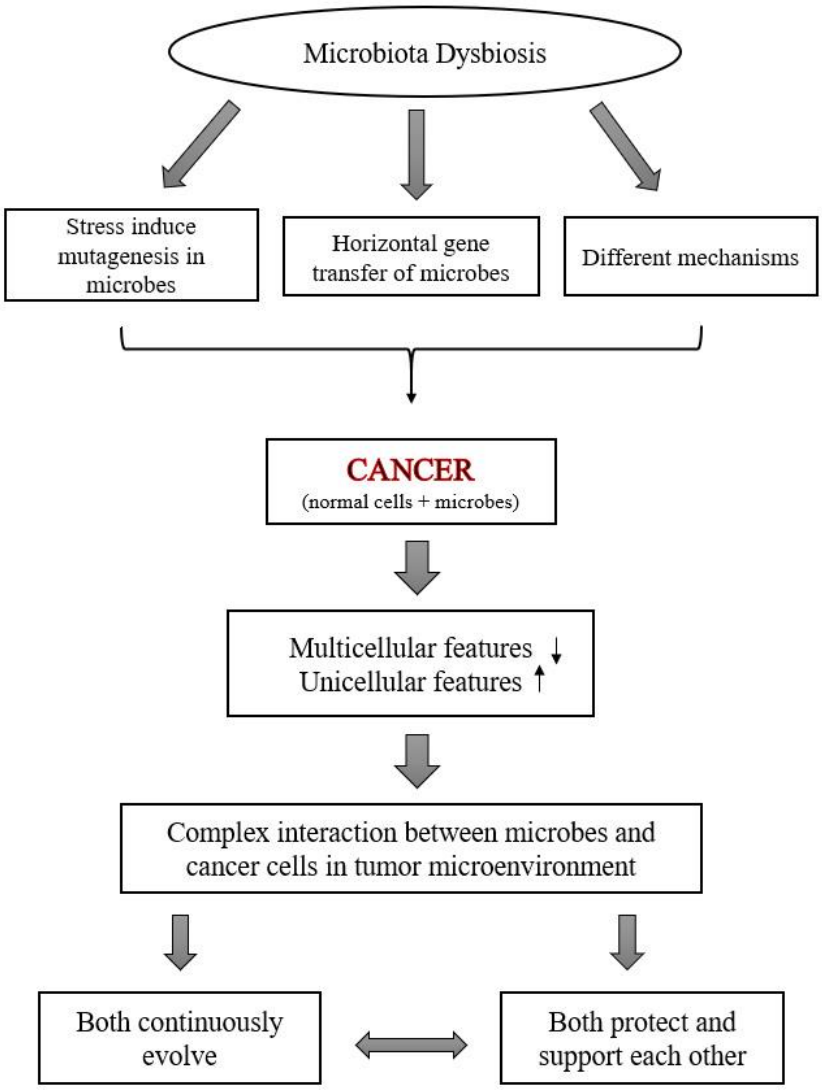

Figure 1: Environmental stress causes microbiome dysbiosis which might cause different defence mechanisms to transfer genetic material into a host's cell. Due to this in cancer, multicellular network downregulates and ancestral unicellular network upregulates. Also, Microbes resides inside the tumor microenvironment and might be forming a complex network to interact with cancer cells.

Lifestyle and cancer

The ecosystem of microbes is rapidly influenced by acute and chronic dietary habits and lifestyle, thereby to maintain a habitual environment for microbes, the importance of a balanced diet has widely come into highlight over the recent decade.[40-42] Certain lifestyle habits like poor diet, stress, and lack of exercise directly affect the gut microbiota, some other factors like age, xenobiotics, drugs, and also environmental changes cause imbalances in gut microbiota equilibrium. Such factors impair the gut microbiota composition and functions, which is known as gut microbiota dysbiosis.[43] There are various recent shreds of evidence supporting the relationship between gut microbiota dysbiosis and cancer development.[44] Some studies also demonstrate the effect of dysbiosis linked with various diseases and disorders, such as inflammatory bowel disease (IBD), ulcerative colitis (UC), obesity, diabetes, cardiovascular disorders, and metabolic disorders.[45-49] Lifestyle and diet are within one's power to improve. There are various factors such as lifestyle, environmental changes, dietary habits, etc. play a significant role in developing cancer. Even a healthy diet plays a vital role, nevertheless, people are moving away from the traditional dietary pattern i.e., Indian dietary pattern, and moving towards consumption of high-fat diets or Western-style diets, which are associated with cancer development and progression.[50] However, the vegetarian dietary pattern and consumption of more plant-based foods, such as fruits, grains, and vegetables have been associated with cancer prevention and overall improve one's health.[51]Therefore, prevention is better than cure.

Microbes, Cancer cells, and Microenvironment

Normal human somatic cells and microbes present inside the body as commensal microbe maintain a healthy relationship with each other, body provide an environment and resources for microbes to live in, they metabolize the nutrients and protect the body from invading pathogens.[33] During cancer formation, this secure environment for microbes no longer stays safe hence results in dysbiosis, the cooperation between normal cells and microbes disturbs thereby cancer cells and microbes to cooperate and enhance each other. In carcinogenesis, bacteria carry out a critical role; they act as carcinogenic and tumor stimulating agents. They possess the capacity to secrete toxins that can convert the signals responsible to regulate a cell.[21] Many bacteria are associated with causing numerous types of cancers, such as *Salmonella typhi* (Hepatobiliary carcinoma), *Helicobacter pylori* (gastric cancer), *Chlamydia*

pneumoniae (lung cancer), *Streptococcus bovis* (colorectal neoplasia and lung cancer), *Escherichia coli* (colon cancer), *Chlamydia trachomotis* (cervical cancer), etc.[22] These bacteria are present not only in the human GI tract but also present in breasts,[23] lungs,[24] ovaries,[25] and prostate.[26]these bacteria play very important role in our body, they help in metabolism of certain compounds and molecules which are usually cannot be metabolize by our body but essential for our body, for instance, dietary fibers. Interestingly, these cancers are the most recurrent cancers among the human population. In stressful conditions, however, these bacteria are currently believed to modify and alter human DNA thereby disturbs the cell cycle, cell death, and increase cell proliferation.[5]Tumor cells continuously evolve inside the ecosystem of the human body, simultaneously they form a microenvironment around the tumor, hence it is called tumor microenvironment. In this microenvironment, there are various growth factors are present to promote cancer progression.[27] Microbes may reside in or near the tumor microenvironment and alter the environment for their convenience by producing factors or bacterial biofilm which influence cancer cell progression.[5] To support this statement, a recent study has discovered the presence of bacterial LPS (Lipopolysaccharide), DNA (Deoxyribonucleic acid), and 16S rRNA (ribosomal Ribose nucleic acid) in cancer and immune cells as well. To a great extent, they argued that different tumor cell types consisted of particular microbial compositions in breast, lung, melanoma, pancreas, ovary, bone, and GSM cancers. After DNA sequencing of bacterial DNA, they found 137 intratumoral bacterial species that are typically associated with various cancers.[28] Therefore, this not only shows a direct relationship between microbes of the microbiome and the formation or development of cancers but also shows the evidence of horizontal gene transfer. Horizontal gene transfer is the movement or transfer of genetic material, like DNA/RNA, between unicellular and multicellular organisms.

The presence of bacterial molecules in tumor cells and behavior of cancer similar to microbes uncoupled novel insights towards horizontal gene transfer (HGT) which shows crosstalk between microbes and human somatic cells during cancer formation. Recent studies have indicated new mediators of HGT which includes apoptotic bodies[29] – apoptotic bodies are a vesicles that contains parts of dying cell – and circulating cell-free DNA.[30,31] These mediators are actively involved in cancer progression and metastasis, as well as drug resistance.[32] Another study suggests, according to the bacterial origin of cancer cells (BOCC) theory, cancer cells arises from the bacteria when the environment in the body is compromised, these bacteria enter

into normal body cells and make a hybrid DNA, further it leads to formation of cancer cells.[20] This theory not only supports HGT but also supports stress induce mutagenesis, during stressful condition, microbes induce drastic changes on genetic level to survive in such condition. It is a survival or defence mechanism. These theories and evidences support during stressful condition and environment, how bacteria are not only involved in progression of cancer but also involved in the process of carcinogenesis.

Microbes promote and initiate cancer through different mechanisms

There are various mechanisms through which cancer cells and microbes influence each other for their survival.[5]Microbes such as E. coli produces some genotoxins like colibactin which induces breakdown of host DNA.[34] Microbes also produce reactive oxygen species that damage the host DNA.[35] Therefore, this results in the formation of cancer. Cancer cells and microbes together not only provide growth factors to each other but also protect one another from the body's immune system. For instance, cells in the tumor microenvironment are no longer capable to divide yet they produce growth factors and bacteria like E. coli is capable of producing toxins such as colibactin which may mediate this signaling pathway and also induce to release of growth factors that promote tumor progression.[36] Typically, microbes in the gut interact with the human immune system but in inflammation, the condition causes bacterial infections which alter adaptive and innate immune signaling as a result of developing cancer.[37] Many microbes use host cells to develop their ecological niches, particularly Fusobacteria invades into a host cell and expand its niche by promoting cell proliferation.[38,39] These reactions of bacteria could be due to the stressful environment for them inside the body, therefore, this might be the defence mechanism of microbes against the environmental imbalances in the host body.

Multicellularity evolution and origin of cancer

The hallmarks for cancers are core principles of tumorigenesis,[15] they provide a unified framework to study the molecular drivers of cancer. Multicellular organisms are evolved from unicellular organisms millions of years ago. Unicellular organisms have basic and simple biological network while multicellular organism evolved and went through various types of variations to form a complex biological network. Although, multicellular organisms still possess unicellular network but it is not in function. So, in cancerous condition, cancer cells

activate the unicellular network and deactivate multicellular network due to genetic alterations.[1] There are many similarities between unicellular organisms and cancer cell such as the fermentation process for cell growth,[16] under the adverse conditions, unicellular organisms employ elevation of genetic instability, which reminiscent of mutator phenotypes.[17] To survive in stressful conditions, the ancient pathways of DNA repair mechanisms such as stress-induced mutagenesis originate in unicellular organisms.[18] The genes associated with cancer are enriched in genes associated with unicellular organisms for conservation, this suggests that during carcinogenesis there is an activation of ancient parts of the unicellular network. This is described as the atavism hypothesis of cancer.[19]

Results from a study suggest that they found a constant progression of tumor cell types similar to pluripotent stem-like conditions, the condition describes the ability of a cell to develop into the three primary germ cell layers of the early embryo and therefore into all the different cells of the adult body, such cell is known as pluripotent stem cells. Further, they proclaim it is a selection of unicellular condition and not the pluripotent condition. Given the fact, coinciding decrease of multicellularity features and increase in primitive features at the cellular level, therefore dependence on primitive unicellular features enhance here. This phenomenon can be activated during cancer formation because core principles of carcinogenesis are associated with the evolutionary history of the cellular and molecular network.[1,2] These studies offer a new direction towards an evolutionary perspective of the original origin of cancer from unicellular life to perceive the behavior of cancer.

Natural selection and Genetic heterogeneity of tumors

Cancer clinically manifests cellular genetic heterogeneity that expresses variation, growth, differentiation, and natural selection. Primarily, tumors were sensitive to certain therapies however, now tumors frequently acquire resistance.[7,4] Many theories suggest that resistance to therapies is due to the natural selection mechanism. Such mechanism operates in various types of cancers, for instance, breast cancer, malignant melanoma, and acute lymphoblastic leukemia.[8-10] During tumor progression, the growth of genetic diversity and heterogeneity seems to be associated with either positive selection or negative selection,[11] because interaction with the surrounding microenvironment is critically essential.[12]This results in the initiation of aggressive phenotype and metastatic behavior. Additionally, the involvement of epigenetic modifications in tumor cell genetic heterogeneity has also been seen, however, this gives

direction towards the non-Darwinian type of evolutionary approach.[13,4] Tumor cells are not solely composed of a genetically mutated cell, but also contain genetically non-mutated cells. All these various types of cells collectively form a complex ecosystem.[14] In this cancer ecosystem, the therapeutic approach initiates novel stimulus, so naturally selecting cells must survive or die. This also suggests that it encourages the chance for surviving cells to proliferate. Therefore, this evolution in tumors represents the noteworthy reason for inadequate results of cancer treatment.[4]

Significant gaps in research

Till this date, it is recognized that cancer cells evolve in the body's ecosystem and so as microbes, also how microbes influence cancer progression and metastasis is known, however, the actual motive of microbes to influence cancer formation is still unknown. Some studies have revealed the presence of bacterial molecules (LPS, DNA and RNA) residing inside the tumor microenvironment but how these molecules invaded the tumor cells and what is the role of these molecules in the tumor formation and progression is yet unexplored. If the involvement of microbes induces cancer to evolves to resist chemotherapeutic drug actions, can antibiotics use in combinations with chemotherapeutic drugs for better treatment? Recent findings have also shown that bacterial molecules are not only present in tumor cells but also present in immune cells, however, why microbes choose to invade specific immune cells and what exact role and mechanism of these molecules in immune cells have with cancer progression is undefined. Cancer is continuously evolving and causing thousands of mutations, but where exactly this evolution will lead cancer to in the future, this aspect is still unanswered. Nevertheless, due to such behavior of cancer yet one critical question is still undefined that are cancer cells new unicellular eukaryotes?

Future directions

In the future, work should focus on understanding the origin and behavior of cancer, and the interaction between microbes, cancer cells, and normal cells. This will present new insights into the possible outcomes in evolutionary pathways of cancer, which will help to understand how cancer can be managed, treated, and prevented in the future.

Conclusion

Natural selection in cancer shows the heterogenicity in the genome of cancer, which is equally responsible for dependence on ancient parts of genes rather than a multicellular network of genes. Cancer can be derived from the unicellular organisms which reside in the human body; microbiome. The human microbiome plays a vital role in cancer progression and development. Microbes reside in or near tumor microenvironment so that they can interact with cancer cells and influence each other to evolve and sustain in the body's ecosystem via various mechanisms. However, a balanced vegetarian diet and a healthy lifestyle possess preventive measures towards cancer initiation.

Glossary

Adaptive immune system – Immunity that develops after exposure to an antigen.
Biofilm – A complex structure of different bacterial colonies that adhere to the surface.
BMI – Body mass index is a measurement of body fat based on height and weight.
Carcinogenesis – A process of cancer formation.
Circulating cell-free DNA – Degraded DNA fragments released to the blood stream.
Commensal microbe – Microbes that supply essential nutrients to host and fight against opportunistic pathogens for host.
Deoxyribonucleic acid – Genetic material in organism.
Epigenetic – The study of how behavior and environment can cause changes that affects the way genes work.
Genotoxins – Chemicals or agents that can cause damage to DNA.
Heterogenicity – Two or more genetic elements that does not have common ancestry.
Innate immune system – Immunity that is naturally present in the body.
Lipopolysaccharide – The outer membrane of gram-negative bacteria.
Metabolism – The biochemical process by which body coverts food into energy to maintain functioning of organs Multicellular – More than one cell.
Metastasis – A process when tumor cells move from main tumor and enter in the bloodstream.
Microbiota – The assemblage of all the different microorganisms that are present in a defined environment.

Microenvironment – Immediate small-scale environment of a group of cells, as a distinct part of a large environment.

Mutagenesis – A process in which genetic information is changed due to mutation.

Phenotype – An observable trait of an individual.

Proliferation – Rapid division of a cell.

Ribonucleic acid – Similar molecule to DNA, act as a genetic material in some unicellular organism.

Signaling pathway – Chemical reactions in which molecules in a cell communicate and control a cellular function.

Somatic cells – Cells of body except sperm and egg cells.

Tumorigenesis – Gradual loss of normal properties of cell and gain malignant properties.

Unicellular – One cell.

Xenobiotics – Chemical substances that are not naturally produce by an organism but found within an organism.

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