

Correlations between Inflammation and Development of Cancer, A Small Review

Abstract

Infection and inflammation are the critical parameters towards developing cancer in the human. Current research interest established that inflammation can lead to chromosomal breakage and development of cancer. Reactive oxygen species (ROS) is one of the key element that takes charge of redox potential followed by protein's conformational change and cancer development. After infection and inflammation, the production of ROS and nitric oxide (NO) activates several cells signaling pathways; which eventually down-regulate some of the essential protein or enzyme's activities. A big range of bacteria and viruses showed the capabilities to initiate cancer. The passive electromagnetic force is also another key element in abnormal gene shuffling during cell division and cancer development. The loss of redox control is the hallmark of cancer formation. People emerged in cell-based therapies that mean training immune cells to battle with microbes. In this paper, several important proteins and enzymes activities are discussed up to subcellular level.

Keywords: Inflammation; Infection; Parameters; Enzyme's; Electromagnetic; Immune cells; Subcellular; Prolong; Carcinogenesis; Angiogenesis; Apoptosis

Review Article

Volume 3 Issue 7 - 2016

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Received: December 07, 2016 | **Published:** December 28, 2016

Abbreviations: HIF: Hypoxia Inducing Factor; NLRP: Nucleotide Leucine Rich Protein; ATP: Adenosine Tri Phosphate; TNF α :- Tumor Necrosis Factor Alpha; AKT: Protein Kinase; mTORC-Mammalian Target of Rapamycin Complex; WNT: Gene Wingless and Protooncogene Integration; MSU: Mono Sodium Urate; PARP: Poly ADP Ribose Polymerase; AIDS: Acquired Immune Deficiency Syndrome; APOBEC: Apolipoprotein B mRNA Editing Enzyme; ROS: Reactive Oxygen Species; PKB: Protein Kinase; NOD: Nucleotide Binding Oligomerization Domain

Introduction

The link between inflammation and cancer was noticed 150 years ago. Inflammation can cause cancer, especially in white blood cells. Prolong inflammation triggers apoptosis, carcinogenesis/angiogenesis and lot more other diseases. The human body produces an enormous amount of T cells and B cells during infection. This is body's immune response and called inflammation. Prolong inflammation can bring secondary inflammation that harms human cells; but without inflammation, human body cannot respond properly against any infection or wound. Microbial toxins such as bacteria, viruses, fungi, protists, and the parasites can produce chemical toxins which trigger body's immune system and inflammation. Physical and chemical injury e.g. exposure to silica, foreign bodies (splinters, sutures, dirt) can cause tissue necrosis [1,2]. In 1911, Peyton Rous reported that viruses can cause cancer. RSV a retrovirus showed v-src gene required to induce cancer in human body. Through reverse transcriptase methodology, RNA virus gets incorporated into the human genome.

Abnormal proliferation of cytokines, interleukins can give rise to several autoimmune diseases. Thus, persistent infection with bacteria or viruses infiltrates cellular homeostasis and incorporate molecules during cell division. Tumor necrosis factor (TNF- α) takes a big part in inflammation and followed by cancer formation [3]. TNF- α has two receptors and activates four major cell signaling pathways.

It is already well searched and diagnosed that some viruses can cause cancer if it lingers in the human body for long. Some viral examples are HPV, Epstein-Barr, Hepatitis, HIV, HHV, HTLV, MCV, SV40 etc. Some of these viruses stay in white blood cells eventually, creates cancer. After a long battle with notorious viruses or bacteria's, white blood cells develop non-Hodgkins lymphoma or another type of cancers. The cellular regulatory system gets down regulated by viral proteins or bacterial proteins. Without inflammation, the human body cannot respond properly against infections or wounds.

Gout

Deposition of uric acid in joints or other areas cause inflammation which is interleukin 1 β mediated. It activates the NOD-like receptor. Antigen presenting cells (APC) can recognize uric acid as a pro-inflammatory molecule which triggers inflammation. Monosodium urate can activate NLRP3 inflammasome, and it regulates interleukin β 1. Chronic inflammation gives rise to cancer, diabetes, cardiovascular disease. Prolong rheumatoid arthritis and psoriasis can create cancer. Muscular, neurological, pulmonary, and Alzheimer type diseases also evolves from chronic inflammation. Monosodium

crystals (MSU) activates other inflammatory cytokines such as TNF- α , IL-6, IL-8, IL-10, and TGF- β etc [4,5]. Prolong gout triggers lymphoma or lymphoma can give rise to gout-like symptoms. Resident macrophage cell lineage senses NLRP 3 inflammasome and release of IL1 β [6]. IL1 β receptor present in synovial cells and in endothelial cells. Adhesion molecules/chemokines take part in neutrophil recruitment and activation followed by more in an inflammatory response. Cytokines and chemokines are small proteins (8-30kD by size). In leukemia, inflammatory pathway starts in bone marrow's microenvironment with nuclear factor kappa B, cytokines, chemokines etc. Inflammation is the great indicator of a certain type of breast cancer. Development of tumor makes breast inflamed, occasional secretion, size enhancement, and change of skin color take place. This type of cancer is aggressive. It fills up lymph nodes in a breast. Itchy rash type of symptoms appears in the skin. Skin is most vulnerable to wounds or inflammation followed by the development of skin cancer. Inflammatory cytokines are over exposed in adipose tissue. When people are suffering from chronic arthritis and gout they show a tendency to develop inflammation to certain types of food. Fungal infection can turn into arthritis as well. Fungal infection such as mold, Aspergillus, Candida can get into lung, mouth, nails eventually, invades into the blood system. It produces joint arthritis.

Signal transduction and development of cancer

Mouth lesion can turn into cancer. Several recent studies indicated that the nuclear factor- κ B is one of the key modulators which convert inflammation into cancer. Signal transducer and activator of transcription, several enzymes also take part in cancer development from inflammatory cells. The microenvironment of inflammation is enriched with macrophages and other leukocytes. Prolong bacterial biofilm in colon and mouth can cause cancer too. Bacterial tissue invasion takes over cellular machinery, followed by abnormal cell division can cause cancer. Mouth, colon, urinary tract are the common spaces of infection where the regular activity takes place.

Cancer starts with reactive oxygen or nitrogen species produced by inflammatory cells e.g., leukocytes causes DNA damage. Chronic inflammation which is not a byproduct of infection can give rise to cancer too e.g.- esophageal, gall bladder and pancreatic cancer [6]. Protein kinase (PKB or Akt) has an immense effect on cancer development. Hyper activation of PKB cells in cancer stroma helps cancerous cells to bypass host immune response. A recent study shows that inhibition of PKB can help to develop cell-mediated cancer therapy. Wnt genes and Wnt proteins are the special type of proteins that carry major signaling pathways. Wnt proteins work via cell surface receptors, whereas PKB acts as an intracellular mediator in the presence of an elevated level of Ca²⁺ [7].

Mitochondrial dysfunction

One of the key parameters that is observed in cancer cells is mitochondrial dysfunction. Reactive oxygen species produced by infected cells causes damage in mitochondrial electron transport chain [8,9]. Some important enzymes get dismantled because of reactive oxygen species and heat. These enzymes are proteins and get encoded from the nucleus of the cells.

Mitochondrial dysfunction and hypoxia inducing factor (HIF-1 α) accumulation found in the tumor microenvironment. HIF-1 α also helps in cancer cell invasion and migration [4,10]. Endoplasmic reticulum (ER) mediated mitochondrial damage or ER stress can trigger inflammation which has nucleotide binding domain with leucine-rich repeated sequence. Some reports also explained that antibiotics and non-steroidal drugs can also produce allergy and inflammation in some human bodies. The sub-cellular level of inflammation in mitochondria takes a big role. Oxidized lipoproteins, uric acid crystals, advanced glycation are the reason for chronic inflammation. Inflammation is also correlated with the early aging process and ROS production. Nlrp3 is a multiprotein complex inflammasome that activates procaspase 1 [3,11-13]. Tumor necrosis factor induces the translocation of procaspase 1 to nucleus. Caspases eventually induces cytokines which regulates cell death or apoptosis.

Blood cancers

Diseases like leukemia, lymphoma and myeloma occur when human body cannot fight with detrimental infection anymore. Bone marrow produces an abnormal number of white blood cells compare to red blood cells. In a case of myeloma, human body stops producing antibodies and make immune system weak. People have noticed chromosomal instability and pervasive DNA damage in multiple myeloma cells. Chromosomal instability comes from abnormal or short cellular division time. Prolong or short attachment of spindle fiber to chromosomes followed by an abnormal number of chromosomes in dividing cells. Cyclin-dependent kinase and PARP are the upstream modulators of homologous recombination and takes a vital role in Myeloma formation [14].

A bacterial pathogen can hijack cell death or cell cycle pathway and determine the fate of a cell. It can also influence cell signaling pathway by manipulating mitochondria's activity. Many bacterial proteins have evolved the technique to interact with host cell/protein in highly specific manner. Bacteria take part in horizontal gene transfer too. Viruses like Herpes deplete mitochondrial DNA followed by mitochondrial dysfunction. RNA sequence study proved the existence of DNA virus and tumor formation is inter-linked in a human. Viruses are not completely carcinogenic but 15% of human tumor is caused by viruses [15-20]. Virus protein takes control over cell signaling and cell growth control pathways. DNA tumor viruses target tumor suppressor proteins. Small DNA viruses like SV40 depends on host cellular machinery to multiply their proteins and DNA.

Parasites

The parasite causes bladder, colorectal and liver cancer [17,19,21]. The egg of parasite triggers inflammation followed by squamous cell carcinoma takes place. Phagocytes release atomic oxygen and nitrogen in infected areas which cause DNA damage in prolonging infected areas of human body. Malaria is linked with Burkett's lymphoma in Africa.

Fungi

Inflammatory bowel disease and gastrointestinal tract infection by Candida produce pro-inflammatory cytokine IL-17 [22]. Generally, it's presence is benign but high level of Candida

produces several gastrointestinal diseases. Presence of *Candida* causes low level of inflammation and it eventually delays healing of lesions. Sawmill workers often get infected by mold followed by inflammation takes place. It is also reported that asthma (a lung infection by) patients face severity when gets infected by fungi [23].

Mitotic cycle and cancer cell energetics

Rapid mitotic cycle causes improper segregation of chromosomes followed by genetical impairment, sticky chromosomal end etc. The demand for rapid production of cellular particles can create a shorter cell cycle, which eventually hampers regular mitosis and produces cancer. Excessive body fluid perturbs cellular ionic imbalance and turgidity. Intracellular electromagnetic field moves the chromosomes from pole to center during mitosis. The electric field of a centrosome in a chromosome causes intracellular energy excitation. People studied the electrical charge of mammalian cells, and it's close to 2-50 MHz. It helps to move the spindle fibers and chromosomes in a cell.

Cancer cell energetics is a good topic to discuss along with normal cells. Generally, mechanical forces are involved in spindle fiber and chromosomal movement. Fluid flow and, electrostatics are the passive forces involved in spindle fiber and chromosomal movement. When electrical current (electrons) is stronger between donor and recipient chromosomes, it causes a break. It's possible to have electromagnetic force between chromosomes and can create cancer [24-28].

Discussion

Viral and bacterial attack

Bacterial and viral protein can linger in the human body for a long period in the dormant condition. Generally compromised immune system brings back the infection.

Viruses and bacteria attack nerve tissues which can linger in the body for a while and eventually damage central and peripheral cells or tissues. Lyme disease, shingles, and AIDS cause extensive damage to central and peripheral nervous system [27,29-33]. The infection starts in peripheral nerve cells followed by invasion into central nervous system. Sometimes it affects blood stream and the main nerve connected to peripheral tissues and microbes; then attack goes to the central nervous system directly. Alpha herpes virus can invade and maintain persistent infection in the mammalian central nervous system. Viruses have that tremendous capacity to stay dormant for a while and revive when body's immune system is weak. The attack in central nervous system diminishes host capability to protect the body from further infections. Peripheral infection and CNS (central nervous system) are separated by blood brain barrier. Cerebrospinal fluid, the brain is separated by several layers of cells; such as endothelial cells, pericytes, astrocytes and basement membrane.

Recent scientific evidence proves that human genome contains 8% retroviral DNA [34-36]. Viruses and bacteria's frequently use horizontal gene transfer mechanism. It would be interesting to see whether a fresh infection utilizes any of the vital DNA or protein that turns into infection inside a cell. mRNA can code viral DNA and

a good molecule to chase after. Teratocarcinoma cell lines showed viral infection can get into germ lines e.g. sperm, egg or placentas. Expression of endogenous retrovirus has reported in several animal tumor cell lines. Horizontal gene transfer is the primary reason for antibiotic resistance development among bacteria's. Horizontal gene transfer also transforms the nonvirulent strain into a virulent strain. Phage virus is an example of horizontal gene transfer where it helps to transfer DNA from one bacteria to others. A viral attack gets difficult to cure when lingers in the human body for a long period followed by a bacterial attack. Two types of tumor forming viruses are present in nature; one is DNA virus and another is RNA virus or retrovirus [37]. Retroviruses carry the tumor-causing gene, but that is not homologous to human proto-oncogene. Dysregulation of the cellular process by viral proteins is also a technique of tumor progression in the human body.

APOBEC

APOBEC is an important human defense protein that takes part in cellular defense mechanism [38,39]. Generally, when this protein mutates, it introduces more mutation in human genome followed by various cancer development in the human body. APOBEC attacks single-stranded DNA. DNA breakage by chemical or environmental factor creates an open fragment. Several viruses contain single-stranded DNA, and it bears the capability to mutate APOBEC. A sub-class of APOBEC cytidine deaminase which converts cytosine to uracil during RNA editing can get involved with retrovirus and retrotransposon restriction activities. Survey showed that APOBEC introduced cancer that was common in head, neck, lung, breast, bladder and cervical cancers (Figure 1 & 2).

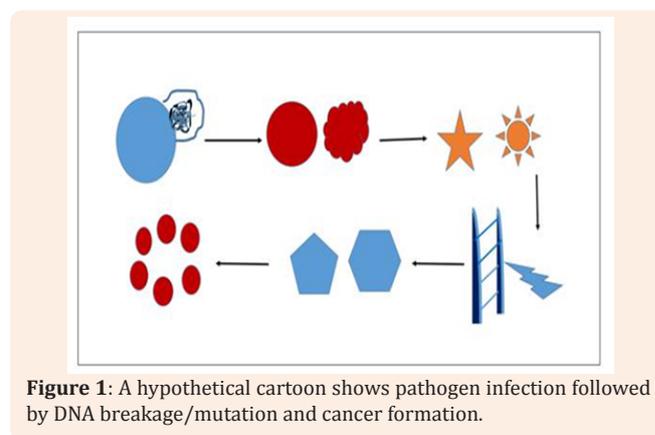


Figure 1: A hypothetical cartoon shows pathogen infection followed by DNA breakage/mutation and cancer formation.

Calmodulin

Calmodulin (CaM) is also another important protein that takes part in various essential subcellular activities such as inflammation, apoptosis, metabolism, short-term and long-term memory, nerve growth cell signaling etc. [40]. It's a major transducer of calcium signal. CaM gets expressed in the cytoplasm, subcellular organelle, plasma, and organelle membrane. Calmodulin can bind to four calcium ions at the same time. Upregulation or down-regulation of calmodulin can be a key part to take care of inflammation and associated cancers (Table 1).

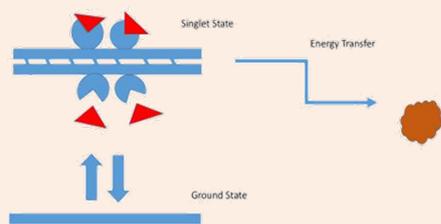


Figure 2: This cartoon shows energy transfer from ground state to singlet. When electron lingers in ground state for long time it creates DNA breakage/chromosomal breakage.

Table 1: List of cancer and inflammation causing agents.

Virus Causes Cancer	Bacteria Causes Cancer	Other Microbes Causes Cancer
Human Papilloma (HPV)	Bacillus anthracis	Candida (fungus)
Epstein-Barr Virus (EBV)	Helicobacter pylori	Clostridium sp. (fungus)
Hepatitis (B, C)	Chlamydia trachomatis	Spiroptera neoplastica (nematode)
HIV	Streptococcus pyogenes	Schistosoma haematobium (parasite)
Human Herpes 8 (HHV)	Mycoplasma sp.	Clonorchis sinensis (flatworm)
Human T-lymphotrophic 1	Chlamydomphila pneumonia	
Merkel Cell Polyoma (MCV)	Staphylococcus epidermidis	
Simian Virus 40 (SV 40)	Leuconostoc lactis	
Adeno Virus	Robinsoniella peoriensis	
Kaposi Sarcoma Virus (KSHV)	Fusobacterium naviforme Prevotella sp. Salmonella typhi Escherichia coli Vibrio cholera Bifidobacterium sp. Listeria monocytogenes	

Presence of oxygen

Normal cells live with plenty of oxygen and a moderate amount of sugar, but cancer cells can survive with almost no oxygen. HIF 1 (Warburg effect, Semenza et al) upregulate several genes that help to survive cells in a very low amount of oxygen. It also helps to generate new blood vessel that is required to establish tumor cells. HIF-1 also activates pyruvate kinase M2 and PKM2 which also helps to produce more glucose. HIFs are DNA-binding transcription factors. Hypoxia can lead to the production of

molecular oxygen/radical in inactive mitochondria [18,37,41]. Hypoxia generated oxygens can lead to the formation of cancer and other diseases. Recently a few HIF-1 α targeted therapeutic treatment launched to treat cancer.

Cancer cell and high energy demand

The high-energy demand of cancer cells gets fueled by ATP (adenosine tri-phosphate) which requires several gene activation and down-regulation of a p53 gene (tumor suppressor protein), p13K protein (oncoprotein). ATP is produced by glycolysis, not the regular oxidative phosphorylation. ATP production by glycolysis is rapid, and it requires cancer cells to uptake glucose even in higher rates. P13K activates AKT which stimulates glycolytic enzymes and mTOR. Initially, it was proposed that mitochondria get defective during cancer development but, later we found that mitochondria remain active in cancer cells [17,18]. Glycolytic metabolism arises from adaptation in the hypoxic environment. Rapid cell proliferation halts without an efficient supply of nucleotide, amino acids, and lipids. PKM2 (pyruvate kinase M2) provides an advantage to cancer cells by slowing down the glycolysis and helps carbohydrates to enter in subsidiary pathways; including hexosamine pathway, UDP-glucose synthesis, glycerol synthesis and PPP. It generates macromolecule precursor for faster cell proliferation. Redox imbalance and hyperpolarized mitochondria are present in cancer cells. The loss of redox control of cell cycle is the hall mark of several diseases such as cancer, inflammation, wound healing, cardiovascular diseases, diabetes etc. In cellular redox chemistry, ROS takes a big part. It produces superoxide (O_2^-), Hydrogen per oxide (H_2O_2) which then reacts with transition metal ion and produces highly reactive hydroxyl radical (HO). It changes cellular redox potential and stress-related signal transduction cascade. Outside stimuli like radiation, a carcinogen, and inflammatory cytokines trigger ROS production [42,43]. ROS alters the activities of protein kinase. ROS causes the formation of intra and intermolecular disulfide bridges; which causes the conformational change in proteins and their activities. Disulfide bonds between cysteine-rich molecules create dimer and multimeric conformation. Eventually, it changes proteins stability, docking sites and receptor-related activities. Several viral studies proved that DNA and RNA viruses (influenza, paramyxovirus, hepatitis B, HIV) generates ROS and causes the activation of monocytes and poly-morpho nuclear leukocytes.

DNA's net charge

We know that DNA's net charge is negative; however the presence of too many negative charges (singlet state oxygen or nitrogen) in intracellular areas might be the reason for DNA breakage. Inflammation induced DNA damage can create mutation which could be the precursor of cancer. People with chronic inflammation have a higher risk of cancer. Some research groups also mention that low energy (ground state) electron attachment causes the break of C-O σ bond (density functional theory) of pyrimidine nucleotides and produces radical anions; which eventually breaks DNA single strand. Singlet oxygen ($1O_2$) species is very reactive with purines, especially guanine base. Oxidized guanine can produce several spiro derivatives which eventually reacts with several molecules. Synchronized oscillation of spindle

fiber creates an electromagnetic field in the cells. People also found that in absence of this higher magnetic field cell develops cancer [36,44-48].

It's a known factor now that nutrient stress causes cardiac inflammation. IL-6 suppresses myocardial glucose metabolism by inhibiting AMPK (AMP-activated protein kinase) and IRS1 (insulin receptor substrate1). Increased glucose uptake takes place in peripheral tissues due to proliferating fibroblast and macrophages in the case of autoimmune diseases [49].

Natural cure

Small peptides have tremendous capability to rupture bacterial cell wall. It can make the perforation in cell wall followed by antibiotic treatment can cure the chronic infection and inflammation. Some common food items e.g. vegetables, tea; wine contains anti-inflammatory molecules or polyphenols. Broccoli, flax seed oil, ginger, garlic, onion are the good sources of polyphenol and omega 3 fatty acids. Polyphenols has an aromatic ring with one or two hydroxyl moieties. Curcumin, resveratrol, capsaicin, catechins, quercetin and vitamins are the key chemical compounds that act as an anti-inflammatory agent [50,51]. Polyphenols can modulate MAPK, Akt, NF- κ B signaling pathways. Probiotics are microbes that help with inflammatory bowel syndrome. A bacteria *Lactobacillus reuteri* helps to reduce mucosal cytokines and takes care of inflammation.

Methodology and Instrumentation

Flow cytometry, confocal microscopy, electron microscopy and cell based *in vitro*, *in vivo* assays are frequently used to study infection and cancer. High-through put screening can be done by a plate reader. RIA, ELISA type of Colorimetric, fluorometric and chemiluminescence are the frequently used cell-based assays in immunology, cancer research and in medical laboratories.

Current flow cytometry instruments carry three laser beams and 13 colors for analysis. With the help of advanced software's, it gets easier to sort out cells from a mixed population of live, dead and broken cells. Abundant usage of antibiotic, polluted environment, drought can cause bacteria to mutate or build resistance against antibiotics. Our future research target would be to train immune cells to recognize antigen or bacteria's' or viruses to overcome antibiotic resistance related issues which appeared recently in several hospitals. DNA library sequencing, mass spectrometry also widely used in immunology and cancer research.

Now PET/CT scanner are commonly used instruments to detect cancer in human body. It's a special x-ray instrument which determines blood glucose metabolism, blood flow, oxygen flow, origin of cancer, the functionality of all organisms etc. For PET (positron emission tomography) nuclear medicine get used and it pinpoints the location of cancer.

Conclusion

Inflammation caused by several microorganisms can eventually give rise to cancer. It's double sided sword that we need to protect our body at the same time prolong inflammation can give rise to cancer. The presence of retro viral DNA in the human genome is

already established. Viral DNA can dysfunction human cells up to subcellular level by producing viral mRNA. It hijacks cell cycle and control cell death phases. Cell-mediated therapy is emerging now, where people can train the human immune system to knock out microorganism related infection and cancer.

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