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Review Article

Gram Negative Bacteria Key Role in the Therapy of Cancer

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Abstract

Bacteria promoting cancer development and tumor progression are gram-negative bacteria like *Salmonella's* species and can play key role in the therapy of cancer. As tumor site are oxygenated so it when systematically gram-negative bacteria rushed into the tumor site, then their necrotic region produced by the reduction of oxygen and declination of nutrients. In the patients of lung cancer, NSCLC mostly, diagnosing the persons which suffer with NSCLC showed that in advanced stage gram negative bacteria play major role in the infection of patients with (NSCLC). In NSCLC patients' infection of lungs along with gram negative bacteria are usually issues after having surgical operation. Assembling proof specify a participation of gram-negative bacteria within the non-small cell lung cancer succession, fundamental processes endure unrevealed. This article would explain the consequence of GN bacteria on the progression of tumor tissues of NSCLC victims. After observance it is concluded that the process of infecting by gram negative bacteria predicted in preliminary stages. The increment and metastasis of non-small cell lung cells caused by incubation by NSCLC with Gram negative bacteria. The mechanism explored that Gram negative bacteria operated tall-like receptor no, 4 which signaling to NSCLC cells, which caused to increase the production of messenger-RNA and expression of protein of interleukin 33 by MyD88-passageway. The destruction of IL-33 revokes the participation of gram-negative bacteria to non-small cell lung cancer succession by controlling cancer metabolic occupation. The increment of IL-33 expression, CD133 expression was directly proportional to TLR4 expression. This information explains the molecular technique of gram-negative bacteria moderate tumor succession.

Introduction

A lot of microorganisms like bacteria, yeast, archaea, protozoa, form a network of ecosystem in human body which ultimately initiates the commensal *microbiota*. Mutualistic relationship form by the combination of commensal microbiota and human host and after this relationship both are able to get assistance. A lot of current research has pivoted the role bacterial component of microbiota. Mode value of number of cells in human body is about 30 trillion which are occupied by 39 trillion bacterial cells [1]. In progressed countries cancer have proved fatal disease [1]. Metastasis which are secondary tumors have previously observed in most of the patients which was facing fatalities. Traditional treatment for cancer attributed by low viability rates because of a lot of factors like tumor development of drug resistance, and these treatments includes chemotherapy and radiotherapy [2]. About more than hundred years back function of bacteria as anticancer agent was observed with a lot of evidences. There are reliable types of cancers which reverted by sudden abnormal erysipelas (*Streptococcus pyogenes*) infection in those patients which hospitalized, these was observations of W. Busch and F. Fehleisen. The case coming from cancer by which one patient undergoing from neck cancer was independently observed by the American physician William Coley, which later began to recover infection with erysipelas. Then he started the use of bacterial toxin for the therapy of cancer [3]. By using destroyed bacterial species, *S. pyogenes* and *Serratiamarcescens*. He prepared vaccine in the end of 1800" s. The earliest examination of automatic tumor regression from simultaneously clostridial infection was reported in 1813 [4]. Researcher has proved that with respect to morbidity and mortality, Gastric cancer lies at fifth position of mostly occurring cancer [3]. Now researcher considering cancer gene therapy very essential part for treatment of cancer by using microbes, the common vector used for the therapy of cancer are divide into bacterial, viral and non-viral vectors [5]. With reference of delivery agents, it was seen that viral vectors proved logical [6]. Use of bacteria vector have special prospective to control restriction of viral vectors by selecting tumors [7].

Mechanism in Which Way Gram Negative Bacteria Helps in the Therapy of Cancer

By declination of nutrients and reduction of oxygen bacteria have ability to produce anti-tumor effects [8]. Anaerobic bacteria for their development form collection in tumor tissues as are deoxygenated in nature. Experiments showed that addition of gram-negative bacteria to the site of tumor via blood vessels cause the necrosis process in that region where proliferation was continued [9]. When gram negative bacteria which are obligate anaerobic started accumulation at the site of tumor then their reduction of oxygen and declination in nutrient particles started, due this phenomenon tumor cells started to dead [9]. Observation showed that for the development of bacterial community condition of tumor may be beneficial [10].

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Role of Gram Negative in NSCLC

Recently it is proved that rate of death in cancer patient is increasing worldwide from which most are patients of lung cancer [11]. From all clinical cases the most prominent case is non-small-cell-lung cancer [12]. Diagnosing process starts within early stage of symptoms [13]. Mostly the patients of cancer are treated with chemotherapy and radiotherapy technique [14]. It showed by scientist that increment and secondary progression of lung cancer of human urged by gram-negative bacteria. The character of gram-negative bacteria inside the continuation of lung cancer is prompted by activation of Toll-like receptor 4(TLR4) [15]. Particularly in those with fencing functions, interleukin33 (iL-33) which is new member of IL-1 super family, showed in different tissue [14]. The formation of Th2 cytokines derived by IL-33 by attaching to its receptor ST2, which play vital role in autoimmunity, inflammation and asthma [16].

Colorectal Cancer and Bacteria

CRC is the third determiner usual type of cancer. There are different methods like radiotherapy, chemotherapy and surgery to treat cancer but not all going well because there is need of more advancements in this strategies Incubation with prebiotic and pre biotic or mixture of both are included in advance therapy of cancer. There are certain bacteria like lactobacillus and Bifidobacteria which give results by increasing their concentration in intestinal microflora this is done by aid of prebiotics and probiotics.Pre- carcinogenic compounds like beta glucuronidase can be hydrolyze by reduction in bacteria enzyme and this strategy has capacity to stop the development of neoplasma by reducing inflammation of intestinal walls, and by increasing immune system [20]. After searching we concluded that by metabolic transformation that imbalance of microbiota in gut is related with CRC threat. At the stage when tumorigenesis occurring, we hypothesize in the microenvironment two separate bacteria which are functionally different. E-*SHIGELLA* and ETBF proved specific capable pro-oncogenic pathogenic which promote tumor genesis [21]. In this article we regulate the microbiota of gut by master plans which have important impact on immune system and microbiota discussion. So there are responses like ant proliferative activity, formation of SCFAS, stopping of toxin producing pathogens etc. showed that gut microbiota manipulation can apply preservative result in opposition to CRC [22]. For the treatment of CRC our discussion suggests that the chances of organizing more sources to neutralize LPS from microbiota of gut .by using antibiotics we can easily do this task by removing of gram-negative bacteria [23].

Therapy of Cancer

Current research studies on model organisms and clinical studies of cell culture showed that gut microbiota change the host response against anticancer microbial agent, and this mechanism accomplished by immunomodulation. For the therapy of cancer dysbiosis is the mechanism which causing multiple response for treatment. New research revealed that mortality rate decreased in those patients which receiving allogeneic hematopoietic stem cell transplant technique (allo-HSCT) for therapy to hematopoietic malignancies by incensement intestinal diversity [24]. T-lymphocytes shows necessary role in the adaptive immune system to play important role to check and manage the presence of cancer cells. Antigen presenting cell emits co inhibitory signal which become cause of activation of T cells. Second costimulatory molecules like cytotoxic T –lymphocyte-associated protein4 play central role in the immune detection system that wet immune response to prevent autoimmune diseases. In the case of cancer cells coinhibitory ligands mostly overexpressed which assist cancer evades immune mediated destruction. FDA-approved immune checkpoint inhibitors stimulate patient's immune response [25]. Gastrointestinal and hepatic issues lie at same stage of immune checkpoint inhibitors with respect to utility [26]. As a result of multiple interchange of immune response microbiota, host genetics and of environment, immune checkpoint inhibitor's side effects are produced, likeenterocolitis, diarrhea, hepatitisetc. Anti-CTLA4 monoclonal antibody therapy results immune-mediated colitis in patients [27]. The importance of changed microbiota in response to prognosis is not clarified, but it is assumed that makeup of microbial communities in patient may be changed with the chemotherapy [28]. When a lot of experimental work performed in mouse models with respect to cancer therapy, then scientist concluded that there is certain makeup of microbiota which effects to the anticancer response of different quality of chemotherapeutics. When patient was treated with platinum chemotherapeutic, oxaliplatin then there was seen tumor declination effects which was engaged by microbiota dependent manner. By using broad spectrum antibiotics microbiota excrete out which ultimately changed expression of genes in host. There were certain pathways like, phagocytosis and antigen presenting pathway which were regulated gene promoting cancer metabolism and cancer development by the process of downregulation. For mediated tumor regression addition of immune cells is very important which decreased by using broad-spectrum antibiotic treatment [29].

Bacterial Role in the Therapy of Cancer

A lot of research on bacteria showed that there are certain bacteria which upgrade tumor and proved carcinogen. The balancing of cellular growth disturbs by toxin produced by bacteria because toxin disordered the cellular signals. As bacteria induced inflammation due to these activities of bacteria, they are called tumor promoter.

There are certain subtypes of bacteria which give rise to cancer, for example in case of gastric cancer *Helicobacter pylori* strain proved cancer causing [30]. Similarly in case of hepatobiliary carcinoma *Salmonella typhi* proved cancer causing strain. Moreover, in pancreatic cancer there are bacteria in oral cavity which secrete peptidyl arginine deaminase which give rise to pancreatic cancer, after this investigation enzymes produced by certain bacteria proved probable carcinogen [31]. With the disadvantage of bacteria as tumor carcinogen, at the same time bacteria proved beneficial factor for the therapy of cancer. There are certain species of bacteria which showed their capacity to engulf cancer tumors, which give rise to declination factor in the growth in the case of neoplasm [32]. After a lot of research in cancer therapy with microbe's scientist showed that subtypes of *Clostridia*, *Bifidobacteria* and *Salmonella* have capacity to colonize tumor infected site to clear tumor cells [33]. As cancerous cells need proper amount of nutrients to regulate their metabolism process, so when bacteria colonize this infected surface, then bacteria showed anticancer effect by declination in the nutrients [8]. There are some tumor tissues which lack the normal level of oxygen, this characteristic of such tumor tissues, look after those species of bacteria which are obligate anaerobic bacteria [34]. Obligate

Table 1: Yearly Non-small cell lung cancer research.

Years	Conclusion
2017	In a specimen to check rate of HIF-alpha mRNA we searched microarray data sets on oncoming and found that level of HIF-alpha mRNA was high as compared to normal lung tissues. The technique use for this experiment was immunohistochemically staining [17].
2018	For the study the effects gram negative bacteria on the increment of NSCLC about 52 patients were tested. When result showed then we found 25 patients positive for gram negative bacteria and 27 were negative [17].
2019	Through gram negative bacteria to NSCLC metastasis TLR4 is applicable therapeutic target [18].
2020	By attenuated pneumonia moves were produced by centrifugation steps. When we check in mice experiment which proceed through nasal drop experiment then we illustrate that this strain with its OMVs was with very low virulence [19].

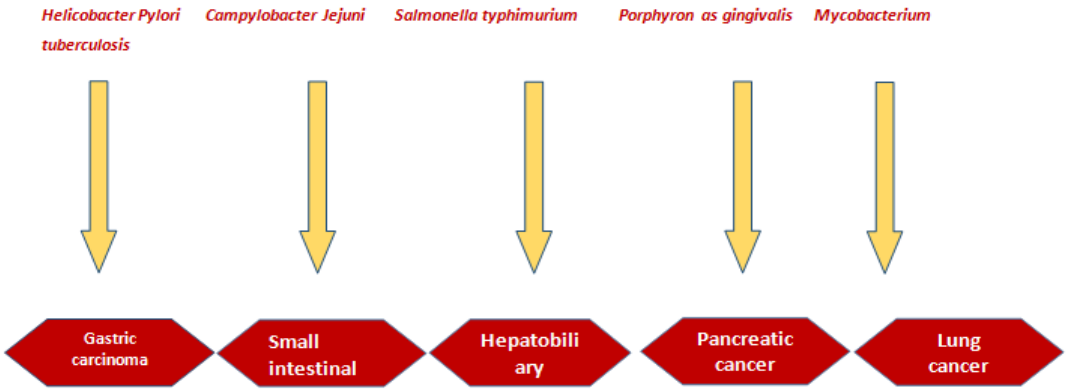

Figure 1: These are bacteria which cause rapid growth of cancer cells.

anaerobic bacteria colonized the deoxygenated tumors which give rise to decrement in the proliferation of deoxygenated tumor cells. In the hemorrhagic area destruction of blood vessels occurs because when there will be declination in the oxygen level and a nutrient then there is formation of necrotic region. This process leads to death of tumor cells due to smother and famine [9]. Cancer therapy with bacteria give rise to bacteria arbitrated tumor treatment which has been launched for centuries. When scientist searched out the side effects of BMTT then it became hurdle for their further development. For the success of bacteria mediated tumor therapy there should be normal fairness between the advantages which comes from BMTT and control infection. Later on, this success of was only attained by the heat inactivation method [35].

Activating Inflammasome Pathways

When signals released from cancer cells then bacterial strain *Salmonella typhimurium* operate inflammasome pathways. Then in the next phase rate of cytokine IL-beta, TNF-alpha and II-18 is enhanced, which give rise to a prominent declination in tumor growth [36]. It has proved that in case of pathogen IL-1beta comes under the list of proinflammatory cytokine which play a significant role in immunity [37]. During animating of multiprotein intracellular complex and tall like receptor (TLR4), IL-1beta is released by lipopolysaccharides, which ultimately source of injury to cancer cells [38].

Gene Delivery Vectors

The system through which gene can be transferred is categorized into biological in which bacteria and viruses comes and into non biological system in which chemical and physical pathway for introduce plasmid DNA to mammalian cells. To the delivery of genes to the plasmid DNA, the system which is used is non-viral gene delivery system. In case of mammalian cells replication of plasmid usually does not occur. There are certain chemicals, like cationic peptides, cationic polymers and liposomes which are used to transfer DNA into cells [39]. To enter the plasmid into the cells, require certain physical and mechanical approaches, for example in the cell membrane to generate temporary hole for the entry of plasmid energy waves are used [40]. There are some pathogenic viruses which have capacity to invade human cells in effective way, they also have ability to express their genes within the cells. Scientist which deals with therapy of genes have make use of the capacity of viruses for the transfer of genetic material (DNA) to cell for the production of protein. Viruses have very systematic benefit as a viral vector because their delivery vehicle process have modified naturally [41]. After using viruses as vector for transfer of genetic material scientist observed a lot of complications, for example many human cancers are with lacking viral receptors similarly in some viral vectors there is size restriction [42].

Bacteria as Gene Therapy Vectors

Bacteria have ability to transfer DNA to cells similar to viruses which act as a delivery vehicle. When utilizing of bacteria as gene delivery vector has started then scientist provide a lot of benefits above gene transfer pathways. Initially when bacteria explored for protectional basis then bacteria lie in the line of non-viral delivery methodology, so far organic nature of bacterial vector explain that a lot of favorable characteristics of viral vector are maintained and these traits are also inheritable [43].

Tumor Targeting Following Systemic Administration

"Gas gangrene" is infection caused by Clostridium perfringens, so retrogression was noticed in tumors of patients which was also associated with "gas gangrene" and it was observed in 1813, and this was first bacteria which have possession on cancer cells which belong to Clostridium genus [44]. Clostridium genus differ by other types of

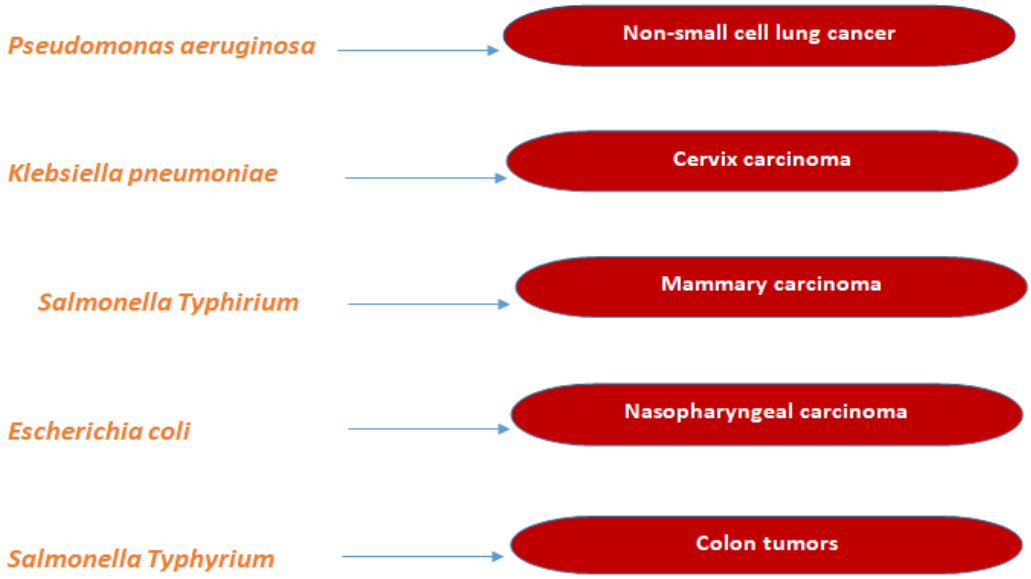

Figure 2: These are bacteria which help in the therapy of cancer.

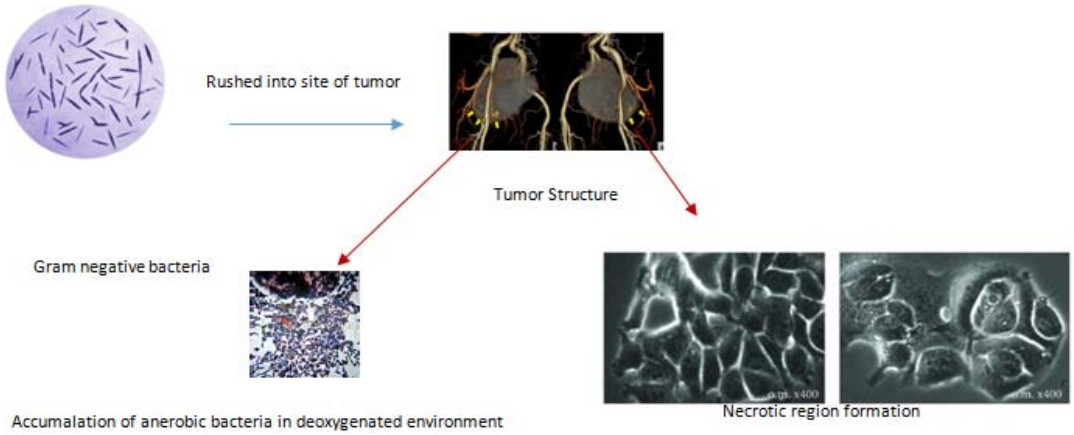

Figure 3: Mechanism of tumor cell death by bacterial.

bacteria due to certain characteristics, for instance they are obligate anaerobes, spore-forming, gram positive. For the germination of *clostridium* bacteria anaerobic environment is required and it will only grow when injected in spore form [44]. For a lot of species of bacteria, for instance Escherichia coli, Vibrio cholera Listeria monocytogenes tumor specific replication four management techniques has been revealed [45]. For the attainment of tumor localized expression, expression of heterologous is necessary and this aspect playing key role even in the non –invasive strains of bacteria. Expression of bacterial transgenes occurs outside the tumorcells. There are encoding factors like, toxins, prodrug-converting enzymes, angiogenesis and cytokines especially along with tumors encoding by amplify genes of different strain of bacteria [46]. Within the four administrations of systematic delivery for certain species there is another option of administration which is oral administration [47].

Process of Tumor Specific Replication

In start those tumors which have lack age of oxygen level was allocated by bacterial colonization of tumors [48]. Solid tumors have special character that means hypoxia originate from very fast-growing tumors with the abnormal supply of blood. Recent study suggested that those solid tumors which suffer from the hypoxia, encourage the growth of facultative bacteria. Purine production from the origin of necrosis encourage the growth of anaerobic bacteria [17]. Quiescent cancer cells have also been recommended as donating part due to involvement of bacterial chemotaxis with regard to chemoattractant compounds which are usually present in necrotic regions [49]. The solid tumors like local immune suppression and aberrantneo vasculature contain distinctive environment with a lot of elements which may be involve to evolve hypoxia theory [50]. Moreover, appearance of tumor selective bacterial species was observed to be tumor origin and bacterial species. Then later it seemed that asymmetrical and leaky nature of blood vessel may be a vital element in this case. Due to asymmetrical nature with improper endothelial linings leakage of blood vessels occurs. In the next step spreading bacteria approach to the tumor tissue due to leaky nature

of blood vessels [51]. Vascularization seen in tumors which would be like lymphatic system of recovery of lesion. In contrast to tumor, in this observation it also seen that bacteria were cleared from the lesion [52]. Insufficient immune system working along with tumors were due to a lot of techniques which were recruit by cancerous cells which assist to safe from perception by the immune system [40].

Misuse Tumor-Specific Bacterial Growth

There are a lot of pathways which can be used to treat cancer by knowing specific colonization of tumors. As they're seen a lot of distinction behavior of bacteria matching with tumors, so due to this activity of bacteria, genetically modified bacteria restricted to tumor site. Bacterial strain also be modified genetically to release therapeutic chemical to target site of tumor in case of noninvasive species. For immune therapy and anti-angiogenesis such cell therapy proceeds towards acceptable specifically for secondary acting therapeutic plan of action. Those bacteria which have invasive characteristics can easily deliver gene to the target site for the therapy of tumor. However, such invasive species have drawback that it can also be invade naturally healthy tissue like tissues of spleen, liver etc., so precautionary statements should be addressed [53]. *Bacterial expression of thymidine kinase along with Positron Emission Topography scanning such gene-based reporter systems also been tested* [54].

Conclusion

A gram-negative bacterium causing to grow tumors rapidly, mechanism is that gram negative bacteria activate TLR9 and TLR4 signaling which increase the production of lipid in cancerous cells of lung cancer. This bacterial mediated lipid synthesis and development of cancer can be block by knockdown of TLR4 or TLR9.Result of experiments showed that where gram bacteria causing cancer their gram-negative bacteria can play key role in the therapy of cancer. A lot of research showed that by using bacteria it would be feasible for the therapy of cancer. Due to side effects, unfortunately this therapy never became casual way to treat cancer. By making combination with other therapeutic treatment bacterial therapy of cancer can play important role in the treatment of cancer.

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