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Review

Microbial Robotics for Cancer Treatment: Review

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Abstract

Cancer is the second leading cause of death in the world. It is essential to find the best strategy and solution as soon as possible. Many therapies such as targeted therapy, immunotherapy, surgery, chemotherapy, radiation therapy, hormone therapy and stem cell therapy are used to treat cancer with new strategies. Still, we need a more advanced strategy to treat it. The use of bacteria in cancer treatment is a new approach. Bacteria can be used as a therapeutic agent. They are used to deliver a nanoparticle to a specific targeted site. The more important thing is that encapsulated bacteria can protect themselves as well as help to reach nanoparticle to its target successfully. Magnetotactic bacteria (MTB) can sense the nutrients and reach there with the help of flagella; it can swim easily through the vascular system. If the nutrient uptake capacity of MTB is increased, it can sense nutrient and attract to the cancer site. The use of MTB with our hypothesis will be the best strategy to treat cancer disease. MTB can be monitored externally with the help of magnetic field. The present review article summarizes the use of MTB as a therapeutic agent and comments on prevention of a cancer.

1. Introduction:

Cancer is a disease in which abnormal cells divide uncontrollably and spread to other parts of the body. Cancer affects the standard mechanism of the body. It also affects the functions of the body parts where cancer has occurred. Mutation in genes of cells can cause cancer by accelerating the rate of cell division and inhibiting the standard control on the system, such as cell cycle arrest and programmed cell death [1]. According to WHO, cancer is a significant public health problem and is the second leading cause of death worldwide. Early detection and early treatment can reduce death numbers [2].

Currently, targeted therapies including, immunotherapy, surgery, chemotherapy, radiation therapy, hormone therapy and stem cell therapy, are used for the treatment of cancer. All therapies work when the cancer is detected in the early stage. We need more advanced and effective treatment for cancer which will help inhibit abnormal cell growth and the proliferation of abnormal cells.For cancer therapy, use of bacteria is a new approach but using bacteria in disease is an ancient method—American physician William Coley[3] known as the first pioneer of cancer immunotherapy. W. Coley used live bacteria to treat cancer. He has used a mixture of *Streptococcus pyogenes* and *Serratia marcescens,* called 'Coley's toxin'. He used colin toxin on patients suffering from inoperable bone sarcomas [3] and observed that tumour growth was regressed [4].

Bacteria are now used to treat cancer; it shows great potential for cancer therapy [3,5]. A vaccine developed by an oncologist from *Mycobacterium bovis* in the late 1980s was for bladder cancer to prevent relapses after surgical removal of the primary tumour [1,6]. This vaccine was generated for tuberculosis [3]. The exact mode of action is not understood, but it is done to increase immunity, like activation of natural killer cell. Most importantly, the delivery of nanoparticles should be targeted. This is because targeted drug delivery involves the death of cancer cells and does not make much difference to the normal cells. Targeted drug delivery reduces the side effects or eliminates side effects [7]. The success of nanomedicines is limited. Microrobots is a solution to overcome these limitations. By using microrobots, i.e., live bacteria, we can deliver nanomedicines to their specific target. We can consider it tumour targeting bacteria.

We can face the challenges using tumour targeting bacteria. Bacillus-Calmette-Guerin (BCG) was used as a therapeutic agent targeting live tumour bacteria. There have been many experiments performed using nanorobots to carry nanoparticle; some are specially designed for cancer treatment. In this review paper, we discussed how bacteria can be used as a robot and which bacteria will be useful for it and possible way for cancer treatment.

2. Bacteria used as a therapeutic agent for cancer treatment:

In bacteria, there is a unique mechanism by which they target solid tumours, which can be used for therapy to differentiate between cancer cells and normal cells [6]. *Salmonella, Clostridium, Mycobacterium* and *Listeria* are examples of live tumour-targeting bacteria used as therapeutic agents [6]. Some bacteria (table 1) are in clinical trials for cancer therapy [11]. Like nanorobots, we can use microrobots for cancer treatment. Nanorobot has the potential to kill cancer cells by taking them to a specific target. Nanorobot detects and repairs damaged organ; nanorobot detects the tumour and destroys them [8].

Table 1: Bacterial species used for cancer therapy [11].

Bacterial speciesand Cancer types
Mycobacterium bovis- Bladder cancer, Prostate cancer, Lung cancer, Melanoma, Metastatic colorectal cancer, Pancreatic cancer.
Listeria monocytogenes- Prostatic neoplasms, Colorectal neoplasm, Metastatic pancreatic cancer, Lung carcinoma, Cervical cancer, Head and neck cancer, Oropharyngeal carcinoma.
Salmonella typhimurium- Neoplasm metastasis, Unspecific solid tumour, Liver cancer, Biliary cancer.
Clostridium novyi- Solid tumours, Malignant neoplasm of lung breast, digestive organs, urinary tract, brain, endocrine glands, and genital organs
Bifidobacterium longum- Solid tumours

We can use *E.coli* as a nanorobot because *E.coli* has flagellum for movement, which allows the microrobot to move quickly through the bloodstream. The electromagnetic field is used to control the movement of *E.coli* [9]. Chemotaxis and magnetotaxis bacteria can easily reach poorly vascularized and hypoxic tumours. These bacteria can easily carry nanoparticles to the tumour [10]. Encapsulated bacteria, if any, protect the immune system from attack. It is imperative to protect any nanoparticle to reach its target safely; this is the specialty of these bacteria; the nanoparticle can be carried to the target without any chemical modification. Encapsulated bacteria can do this mechanism very quickly. *S. typhimurium* is a therapeutic bacterium encapsulated in biocompatible or biodegradable alginate microbeads [10]. Since it is a pathogenic bacterium, it can affect the other normal cells in the body. By making the bacteria avirulent, we can use this bacterium regularly as a therapeutic bacterium for cancer treatment.

Magnetotactic bacteria (MTBs) have a sensory element present, which guides them to a specific region called aerotaxis. Aerotaxis, a form of energy taxis, is an active cell movement along gradients of oxygen [11,12]. Magnetotactic behavior helps them to search nutritional requirements [11]. Since flagellum is present, these bacteria can easily swim in any part of the body and using the same mechanism; we can get the nanoparticles to that point. It is a bit difficult to grow MTB in laboratories. *Magnetospirillum gryphiswaldense* MSR-1 and *Magnetospirillum magneticum* AMB-1 species were first isolated from freshwater. MTB is an aquatic motile and non-pathogenic bacterium [11]. MTB are the best options because they are surrounded by a biocompatible organic envelope, which protects them from the attack by the immune system. Another positive thing about MTB is that they have the capacity of self-propulsion, for which they are helped by flagella. These bacteria can guide and manipulate external magnetic fields and attract a hypoxic area like a cancer site [11]. However, magnetotactic bacteria, are challenging to grow in the laboratory [13].

3. Microbial robots-a tumour targeting bacteria:

By using microrobots (live bacteria), we can deliver nanomedicines to their specific target. The reason behind considering magnetotactic bacteria is that they have flagella for their movement. Magnetic fields can be used to control such bacteria. These bacteria have a coating, which protects them from the attack by the immune system. The magnetotactic bacteria can be used as a therapeutic agent to carry nanoparticles to the cancer site.

Cancer cells need a lot of nutrition, so there are plenty of nutrients present where the cancer is present. If magnetotactic bacteria are genetically modified to increase their nutrient uptake capacity, they can go to the cancer site and uptake the nutrient there. Magnetotactic bacteria have sensory elements, and as a result, they can sense the nutrient-rich site and get attracted towards it.

These bacteria will go there and perform two mechanisms (figure 1). First, these bacteria will reach there and release nanoparticles. Nanoparticles start working against cancer cells and destroy them. Second, by increasing the nutrient uptake capacity of these bacteria, they will reach the cancer site, absorb the nutrient, and the cancerous cells will die due to the condition of nutrition starvation.

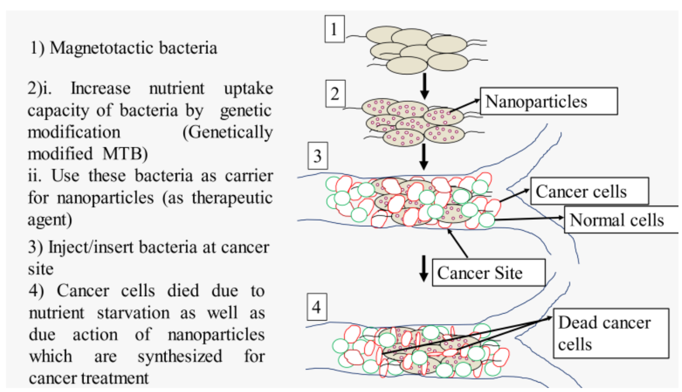

Figure 1: Mechanism of Genetically Modified magnetotactic bacteria (MTB) against cancer.

4. Conclusion:

Bacteria can be used as a robot for cancer treatment. In future, chemotaxis and magnetotaxis bacteria may be very useful to treat cancer. Nanorobots are monitored externally to reach the cancer site. Like nanorobots, MTB can also be monitored externally with the help of magnetic fields. It can lead these bacteria to a specific targeted site.These bacteria can be used as carriers to carry nanoparticles to treat cancer.

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AJ: Developed an idea and wrote the manuscript. SS: Improved the manuscript and Verified the data. NB: Corrected the manuscript

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The authors declare that no conflict of interest exists regarding the writing of this article.

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