**Title: The Effects of Salmonella typhimurium on Cancerous Tumors**

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**Key Words:**

Stem cell, transcription factors, mesenchymal, stem cell therapy

**Abstract**: **Every year millions of people throughout the world are diagnosed with cancer, which has caused researchers to focus their efforts on finding more effective treatment options. This study focuses on the efficacy of treatment using a genetically modified strain of Salmonella typhimurium. Current treatments involving strains of Salmonella have had promising results, however; they are not effective long term treatments and tumors have a tendency to recur. In their study, Zheng et al attempted to modify a bacterial strain so as to make it more efficient in its ability to cause long term tumor repression. The researchers are trying to determine if cancerous tumors can be broken down in response to injection of S. typhimurium in to the tumor. Furthermore, they wanted this immunological response to only be triggered during the desired time and at the desired location. The researchers are hoping that specific flagella present on S. typhimurium will be effective at activation of the toll-like receptor(TLR) signaling pathway. The researchers tested the activation effect of S. typhimurium on TLR4 and TLR5 to determine how it interacted with different kinds of TLR. In order to test their hypothesis, they genetically altered S. typhimurium, and injected it directly into the tumor in mice.**

**Introduction**

Cancer is the unregulated proliferation of tissue cells in the body, causing tumors, which can spread throughout the body causing multiple cancerous sites. According to the CDC, cancer is the second most common cause of death, with numbers close to 600,000. Additionally, 20.3 million adults have been diagnosed with cancer to date, which is roughly 8.5% of that the population [1]. Due to these factors, it is imperative that a more effective treatment option is made available to those suffering from this disease. Due to the abnormal tissue growth in cancers, many areas of these tumors are made up of dead tissue. This makes them an ideal growth environment for facultative or obligatory anaerobic bacteria, such as S. typhimurium. A modified strain of S. typhimurium was injected into tumors in mice to determine the effect this strain will have on the immunological response to tumors [2]. The results from this experiment indicated a significant decrease in tumor size after injection.

**Recent Progress**

Current cancer treatments, while fairly effective, are in need of improvement. In order to bring about this improvement, many researchers have attempted bacterial cancer therapy (BCT). They administer bacteria into cancerous tumors and use that environment to stimulate the proliferation of bacteria. The point of BCT is to trigger an immune response from the host in order to cause the body’s innate immune system to fight the cancer on its own. It also causes the tumor cells to be more sensitive to chemotherapy [2]. Unfortunately, while there has been some progress made in this area, there are multiple problems with BCT. Namely, there is a lack of longevity in tumor repression and recurrence is common. Additionally, they have encountered problems due to toxicity from injection of a large number of bacteria.

In his study, Zheng builds his experiment based off of the results of previous studies by prior researchers. He mentions that in recent studies, strains of S. typhimurium have been used with varying gene deletions. While these were effective at initial treatment, they required multiple injections of the bacteria and failed to stop the tumors from recurring during the trials [2]. These were the issues that Zheng addressed throughout this study.

In an effort to increase the efficacy of the treatment, they genetically modified S. typhimurium to secrete flagellin, specifically flagellin B(FlaB). FlaB was chosen due to results from previous testing, which indicated that it triggers activation of innate immune response. The activation is because FlaB is a ligand that causes activation of the TLR signaling pathway. Activation of TLR signaling pathway causes proliferation of macrophages and neutrophils, which both secrete signaling proteins that contribute greatly to the process of breaking down the cancerous tumors [2].

According to Zheng, a common concern for use of BCT is that it would only be effective for treatment in cancer tumors that express the TLR5 signaling pathway. Dependence on TLR5 would prove problematic for treatment as many forms of cancer occur because of a lack of TLR5.

In order to address this concern, Zheng et al injected the modified S. typhimurium in to tumors in mice. They ensured a high viral count through bioluminescence imaging [2]. This allowed them to ensure a significant amount of bacteria were growing in the tumor. After sufficient growth was determined, they measured the tumor size in mice every 3 days for 50 days. In addition to tumor size, they also examined the effect their strain had on general TLR activation. Zheng et al measured activation effect through observation of TLR expression after introduction of the FlaB. This gave them the ability to verify the effect of FlaB on TLR [2].

When they observed the toll like receptor pathways, they found that both TLR5 and TLR4 were activated through secretion of FlaB [2]. In order to determine the importance of each, they knocked out the genes that coded for TLR4 and TLR5 separately. During this testing, Zheng et al determined that mice expressing only TLR4 genes responded more favorably to the treatments than did mice with only TLR 5 genes [2]. The data from this test worked to nullify the concerns of critics due to observed activation of TLR4 and TLR5. Activation of members of the TLR family is vital for effective treatment due to their effect on proliferation of macrophages and neutrophils in the tumor itself.

The final problem they were concerned about was the toxicity to the body. This was caused by high levels of concentration of the bacteria. In order to test this, they allowed the S. typhimurium to colonize the liver and spleen. The researchers then induced tumor growth in the mice. 3-4 days after tumor growth began, the population of S. typhimurium decreased rapidly and began proliferating in the tumor [2]. This finding shows that the modified strain of S. typhimurium should cause minimal toxicity in the host, if any at all.

**Discussion**

The researchers in this study were thorough in their examination of their study. Their study indicates the possibility that S. typhimurium could be a valid alternative for cancer treatment pending more research. Despite their study not giving indications of significant toxicity due to BCT, more rigorous testing is necessary to completely rule it out as a possible problem in this treatment option. One problem with this study would be the lack of cancer types tested. In order to know if this could be a widely used treatment option, then they need to know the efficacy of it as it pertains to the many cancer variations. Due to the positive results obtained in this experiment, Zheng et al has produced a possibly viable alternative that requires further testing by other researchers in order to verify the validity. Pending the results of their study being replicated by other researchers, Zheng et al could have potentially found a viable addition to the course of treatment for cancer patients.

**References**

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