PART II: BREAKTHROUGHS IN TUMOR-SEEKING BACTERIA

Newly engineered bacterial strains propel an immune-mediated cancer therapy toward clinical applications. Hannah Martin Lawrenz reports on the latest developments.

Scanning electron microscopy image of *Salmonella* strain SF200. Bacteria are stained in dark blue and outer membrane vesicles in light blue. Credit: Manfred Rohde, HZI.

In the fight against cancer, researchers have recruited an unlikely ally—a strain of *Salmonella* that causes food poisoning. Previously, scientists attempting to hijack this pathogen in order to target cancer struggled to balance its aggressive therapeutic actions and its harmful attacks on healthy body systems. Now, a team at the Helmholtz Center for Infection Research in Braunschweig, Germany proposed a more precise way to attenuate and strengthen this tumor-fighting technique.

“Understanding the basic immune aspects of bacterial therapies is critical for translating the technology for synthetic biologists like myself,” commented Tal Danino at Columbia University, who wasn’t involved in the Helmholtz studies. “This is great research.”

Hijacking a Versatile Vehicle

When they began their studies, researcher Sebastian Felgner and the Helmholtz team planned to use *Samonella* as a carrier for vaccines in mouse models, but they soon realized that the bacteria naturally homed to tumors and could attack cancer successfully. Since the team already had suitable strains available, they redirected their focus to tumor-targeting studies.

First, Felgner established some advantages of using bacteria-mediated tumor therapy compared with conventional methods such as surgery or chemotherapy (1). However, “the greatest challenge was, of course, integrating the safety profile of the bacterial strain with therapeutic potency,” said

Felgner. “We think we’ve made a tremendous step forward in this matter.”

Using virulent strains of bacteria for systemic cancer treatment can cause severe side effects such as weight loss and damage to healthy organs (2). To mitigate these risks by limiting the bacteria’s dissemination throughout the body, the scientists locally applied *Salmonella* Typhimurium within colon tumor-bearing mice and mice with resistant fibrosarcomas. This local approach improved safety while retaining the cancer-fighting benefits observed using systemic intravenous applications of bacteria. In fact, the therapy’s accuracy improved enough to allow targeting of secondary or potentially surgically inaccessible tumors as well.

Through genetic engineering, the researchers developed a stronger *Salmonella* strain, which became their focus in subsequent studies. “Although we incorporated known single mutations, their combination created an unexpected phenotype that significantly increased the efficacy of our strain, SF200,” Felgner explained.

Anticipating Real-world Challenges

Next, the researchers deployed SF200 in mice with anti-bacterial immunity, anticipating how the anti-tumor bacteria might behave in humans, pets, or livestock that are sensitized to *Salmonella* (3). They tested the same concept using *Escherichia coli*, as this close relative of *Salmonella* is commonly encountered by humans and has an established safety profile.

Schematic of the hypothetical process of solid tumor invasion and colonization by *Salmonella*. Credit: S. Felgner.

"Our idea is to attenuate *Salmonella* and, if necessary, to arm *E. coli*," explained Felgner. "This should give us more options for using the bacteria in human cancer patients."

As expected, pre-exposure to *Salmonella* or *E. coli* impaired the therapeutic effectiveness of the bacteria. After comparing systemic and local applications of both bacteria, the team realized that overcoming potential immunity would require further modifications of bacterial-associated immunogenicity factors using genetic manipulation.

"Our *Salmonella* and *E. coli* strains activate cytotoxic T cells involved in tumor clearance," Felgner noted. "Thus, when we realized the bacteria's adjuvanticity was exclusively responsible for therapeutic efficacy, we knew it was possible to lower the bacteria's virulence while strengthening its immunogenicity."

Looking Ahead

Although the exact mechanism of bacteria-mediated tumor therapy is still unknown, "It appears to be due to a com-

bination of a direct and an adjuvant effect of the bacterial vector," said Felgner. These findings could prompt other scientists to devise bacteria-based strategies against different types of cancer.

Going forward, the researchers will deploy SF200's unique balance of efficacy and adjuvanticity for upcoming clinical trials in collaboration with Mantis Therapeutics.

References

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