200 years ago the observation was already described that tumors sometimes shrink when cancer patients undergo bacterial infections. This is the basis for bacteria-mediated cancer therapy - an alternative therapeutic approach of growing interest. Several bacterial strains are able to colonize solid tumors after systemic administration; a few even induce tumor reduction. Apparently, the virulence of bacteria is crucial for an anti-tumor effect. Now the major challenge is to tailor bacterial strains that combine safety with therapeutic efficacy.

History

At the beginning of the 19th century, Vaultier noticed that bacterial infections of cancer patients were associated with shrinkage of the tumors [1]. A first report of intentional treatment following this groundbreaking observation dates to the year 1868. The German physician W. Busch placed a woman with an inoperable sarcoma into a bed that had been occupied before by a patient suffering from erysipelas - a Streptococcus pyogenes infection. The woman successfully became infected and her tumor shrunk. Unfortunately, she died of the infection nine days later [2]. The toxicity of bacteria could not be handled at that time. Therefore, similar attempts with different bacteria or bacterial products - like the well known Coley's toxin - failed, despite some success regarding the anti-tumor effect. Nowadays, the situation has dramatically changed. Knowledge about host-pathogen interactions, the genome information of bacteria as well as state of the art molecular methods allow modulation of bacteria for particular purposes. Hence, the approach of using bacteria in tumor therapy presently undergoes a renaissance and is under intensive investigation.

Different types of bacteria can colonize tumors

Amongst the bacteria that are able to target and colonize tumors are obligate anaerobics like Clostridia and Bifidobacteria but also facultative anaerobics like E.coli
or Salmonella. As it is a characteristic of most solid tumors to have regions of low oxygen, it appears reasonable to use bacteria that can only grow under hypoxic conditions. This would avoid adverse effects on healthy tissues. However, it is just this specificity which limits the potential of obligate anaerobic bacteria. They will leave well-oxygenated tumor areas unharmed from which the cancer can re-grow. In contrast, facultative anaerobic bacteria should have the potential to colonize all areas of a solid tumor and thus exhibit a stronger anti-tumor effect.

**Entering the tumor**
Although it could be shown for various bacterial strains that they can colonize tumors, it is still not absolutely clear how they manage to enter the cancerous tissue. This is a crucial point as an efficient anti-tumor effect demands sufficient colonization. Different scenarios of the entry process can be envisioned. One suggests an active mechanism where bacteria are chemoattracted by substances of quiescent or necrotic tumor cells [3]. Alternatively, we propose that bacteria are passively flushed into the tumor tissue through its leaky vasculature. Upon intravenous application of S. Typhimurium to tumor-bearing mice, a rapid and strong influx of blood into the tumor can be observed (fig. 1). At the place of this hemorrhage, a huge necrosis forms. *Salmonella* are colonizing this part and the region bordering the viable tumor rim. TNF-α was identified as one mediator that plays a crucial role in this process [4]. We consider this an important finding. Clinical studies with an attenuated mutant strain of S. Typhimurium exhibiting a diminished potential to induce TNF-α showed only very poor tumor colonization in human cancer patients [5]. Thus, the challenging task is to generate mutant strains that are virulent enough to efficiently colonize tumors and at the same time attenuated enough to be safely administered.

**Controlled expression of therapeutic molecules**
Particular bacteria do have anti-tumor effects when administered systemically. Apart from this natural ability to cause tumor shrinkage, they can also be used as vectors to deliver therapeutic molecules directly into the tumor, thus enhancing killing of the cancerous cells. These molecules could be bacterial toxins, cytokines that activate an anti-tumor immune response or prodrug converting enzymes. Independent of which protein to be expressed, it is essential that the mode of expression can be controlled tightly to prevent adverse effects on healthy tissues. This could be achieved by the use of special promoters to drive expression, like inducible promoters. An example would be the E.coli promoter $P_{BAD}$ that can be induced by the sugar L-arabinose (fig. 2). Administration of this sugar to mice infected with bacteria that encode the therapeutic molecule under control of $P_{BAD}$ expression can be started at any defined time point [6]. Other possibilities are the use of in vivo inducible promoters. For instance, we have defined several promoters that respond to the special physiological conditions of the tumor tissue but are silent in other organs. Therefore, the expression of a therapeutic molecule can be rendered tumor specific. Using these control elements, the expression of the potentially toxic substances in healthy tissues should be prevented leaving them unharmed by the therapy.

**Conclusion**

Many different bacteria have demonstrated their potential to be used in cancer therapy as they are targeting solid tumors. However, the demands for an ideal anti-cancer bacterium include more than that. It has to be safe and efficient at the same time. A combination that appeared to be unsolvable when this therapy had been applied first more than 100 years ago. With today's knowledge and the possibilities of molecular genetics to tailor bacteria to the very special purpose, a successful application of bacteria in cancer therapy appears to be in reach.

**References**


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