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Cover Story

Tissue penetration of bacteria into quiescent regions of tumors

In this issue, about half of all research papers deal with tumor-targeted drug delivery using various carriers. Currently, most targeted drug delivery is based on non-living carriers. Inactivated live viruses have been used for gene delivery, but several deadly outcomes shifted focus to non-viral systems. The non-living delivery systems, however, have one critical deficiency. Once out of the convective flows of blood and interstitial fluids, drugs and carriers depend on diffusion to reach target cells. Regions that are far from vasculature do not receive drugs at sufficient concentrations. Here, the idea of using motile systems, such as bacteria, becomes attractive. When delivered as live organisms into the blood stream, bacteria actively penetrate into tissue. Motility-based penetration enables treatment of resistant regions that are unreachable by diffusing molecules.

To envision live bacteria as drug carriers, it is necessary to understand how these therapies would function in a clinical setting. Therapeutic bacteria would not carry drugs in the traditional sense. While it is possible to insert molecules directly into inactivated bacteria, it will not be therapeutically useful. Live bacteria depend on proliferation as one of the mechanisms that promote tumor accumulation. Drug molecules would be quickly washed out after several generations. Therapeutic bacteria are typically injected at low doses, around 10^8 organisms/kg, and rapidly proliferate to densities many fold greater, often in the order of 10^9 organisms/g tumor. For this reason, bacteria must deliver therapy via their genetic material, which is replicated during mitosis. Therapeutic proteins are encoded into the genome or on plasmids [1]. When triggered, colonized bacteria synthesize these protein drugs and secrete them into the local environment [2].

In a paper in this issue [3], Zhang and Forbes quantified mechanisms of bacterial migration in tumors that, to date, have been largely unexplored. They show that the bacterial sugar receptor, Trg, plays a critical role controlling where Salmonella accumulate in tumors. They did this by deleting the trg gene from the genome of nonpathogenic *Salmonella* and then measuring the behavior of individual bacterial in a tumor-on-a-chip device and in mouse tumor models. They found that deleting the Trg chemoreceptor amplified accumulation in therapeutically resistant quiescent regions. Trg is the primary receptor *Salmonella* use to sense and migrate toward external sugars, specifically glucose, ribose and galactose. Knockout trg-bacteria cannot detect sugars (primarily glucose) in nutrient-rich environments near blood vessels. For knockout organisms, random dispersion has a greater effect on their migration patterns allowing them to slip deeper into tissue. Wild-type bacteria, with active receptors, are attracted to sugars and do not migrate away from vessels.

Zhang and Forbes also show that bacteria have three distinct lifestyles in tumors that control colonization. They observed that bacteria are either penetrating, proliferating, or inactive. Most colonized bacteria are sessile and not proliferating. A small percentage of the population penetrates deep into tissue, colonizing regions that are hundreds of micrometers away from blood vessels. Another small group grows into large colonies that are located near vessels. For bacteria-based therapy to be effective, the sessile population has to be eliminated to increase penetration and reduce heterogeneity. The dominant presence of a sessile population may be a reason for failure of *Salmonella* colonization of tumors in preliminary human trials [4]. Understanding how *Salmonella* penetrate and target quiescence is an essential step toward creating a tightly controlled, tunable bacterial therapy. The results presented by Zhang and Forbes will open the door to new avenues of research, and will encourage more exploration into the use of bacteria as delivery agents.

While bacterial strategies require further studies to be clinically useful, the idea of using motile system can be extended to non-living delivery systems. Can we develop non-living, but motile systems to solve the transport limitations that have troubled the delivery community for many years? It will be very difficult to develop any nonviable delivery systems that actively penetrate. All breakthroughs for seemingly impossible problems, however, start with a simple question, why not?

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