Review

Diffusion-Controlled Therapeutic Delivery via Engineered Bacterial Biofilm Scaffolds in Oncology

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Diffusion-Controlled Therapeutic Delivery via Engineered Bacterial Biofilm Scaffolds in Oncology

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Abstract

Bacteria-based cancer therapies have re-emerged as a promising modality due to the intrinsic capacity of certain bacterial species to preferentially colonize hypoxic and necrotic tumor regions [1,2]. However, planktonic motile systems are frequently limited by rapid immune clearance, transient persistence, and uncontrolled payload release [2,3]. This review introduces a synthetic biology framework that reframes bacterial biofilms from pathological barriers into programmable therapeutic scaffolds. By utilizing programmable microbial therapeutic chassis, researchers can enhance therapeutic duration within the tumor microenvironment (TME) while potentially minimizing systemic exposure [4,5]. Central to this framework is the genetic modulation of matrix density, primarily via curli fiber-associated *csgA* expression. This approach may enable drug release kinetics governed by Fickian diffusion principles, allowing for sustained and controllable therapeutic delivery [6,7].

Keywords: synthetic biology; biofilm engineering; tumor-targeting bacteria; synthetic microbial therapeutics; biocontainment; *csgA*; diffusion-controlled drug delivery

1. Introduction

Modern oncology continues to face significant challenges regarding the selectivity and localized delivery of therapeutics [8]. Bacteria-based therapy exploits the natural tumor-homing capacity of certain species as part of emerging bacterial therapeutic strategies [4,9]. However, the translational success of these systems depends not only on targeting efficiency but also on achieving a sustained and controllable therapeutic presence without inducing systemic toxicity [1,10].

2. Limitations of Current Planktonic Systems

Existing therapies primarily rely on planktonic motile bacteria. Preclinical evidence suggests these systems often suffer from rapid immune recognition and are typically cleared within 48–72 hours following administration [3,11]. The absence of a protective structural matrix renders individual bacteria susceptible to phagocytosis and complement-mediated killing, which may lead to suboptimal persistence in the tumor core [11,12]. Furthermore, uncontrolled payload release in these systems often results in burst kinetics that can increase the risk of off-target toxicity [13].

3. Biofilms: From Clinical Obstacle to Therapeutic Opportunity

Historically viewed as pathological barriers, biofilms offer unique opportunities for synthetic biology engineering [14,15]. Within the TME, biofilm-associated bacteria are expected to achieve prolonged persistence compared to planktonic counterparts due to EPS-mediated immune shielding [4,11]. Advances in genetic circuit design now enable the precise regulation of matrix assembly, effectively transforming biofilms into programmable biological scaffolds [6,7]. However, the inherent complexity of biofilm development requires rigorous control to prevent unintended tissue obstruction, vascular occlusion risk, or localized inflammatory overload [14,15].

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4. Engineered Biofilm Scaffolds: The Conceptual Framework

This framework involves the design of bacterial biofilms as stable, long-lived therapeutic structures within solid tumors [4]. Programmability is achieved by integrating synthetic regulatory elements, such as hypoxia-inducible or pH-responsive promoters [6,10]. By modulating the expression of curli fibers via *csgA* regulation, the effective diffusion coefficient (D_eff) of the matrix can be genetically tuned, enabling therapeutic release kinetics consistent with Fick's law [7,13]:

$$J = -D_{eff} \partial C/\partial x$$

where D_eff reflects matrix porosity and cross-link density. This relationship may facilitate controlled therapeutic payload delivery, ensuring that the payload is released at a predictable rate rather than through spontaneous burst release.

5. Biosafety, HGT, and Biocontainment

For clinical viability, biofilm scaffolds must incorporate multi-layered biosecurity protocols [16]. A critical consideration in biofilm engineering is that dense microbial communities may increase the risk of horizontal gene transfer (HGT), necessitating integrated biocontainment switches. Biofilm-associated close cellular proximity may further facilitate genetic exchange, reinforcing the need for robust genetic isolation. Beyond simple lysis circuits, strategies including engineered auxotrophy and "deadman" switches are essential to prevent HGT and unintended environmental persistence [6,16].

6. Experimental and Translational Roadmap

Validation of this framework requires a transition from traditional 2D cultures to biomimetic models. Microfluidic "tumor-on-chip" systems are proposed to replicate the physiological flow and oxygen gradients necessary for biofilm maturation [4,7]. These platforms allow for the real-time quantification of payload diffusion as a function of genetically tuned matrix porosity [12,13]. Future clinical translation requires the integration of regulatory science, host-microbiome interaction studies, and scalable GMP-compatible microbial engineering pipelines.

7. Conclusions

Engineered biofilm scaffolds represent a conceptually distinct paradigm shift in bacterial cancer therapy. By integrating advanced biocontainment strategies with diffusion-controlled release principles, this framework holds the potential to improve localized cancer treatment outcomes and durability. Further experimental validation will determine clinical feasibility and the ultimate safety profile of these systems.

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