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Pitfalls and promises of bile duct alternatives: There are plenty of room in the regenerative surgery

Klabukov ID *et al*. Plenty of room in regenerative surgery

Abstract

Current abdominal surgery has several approaches for biliary reconstruction. However, the creation of functional and clinically applicable bile duct substitutes still represents an unmet need. In the paper by Miyazawa and colleagues, approaches to the creation of bile duct alternatives were summarized, and the reasons for the lack of development in this area were explained. The history of bile duct surgery since the nineteenth century was also traced, leading to the conclusion that the use of bioabsorbable materials holds promise for the creation of bile duct substitutes in the future. We suggest three ideas that may stimulate progress in the field of bile duct substitute creation. First, a systematic analysis of the causative factors leading to failure or success in the creation of bile duct substitutes may help to develop more effective approaches. Second, the regeneration of a bile duct is delicately balanced between epithelialization and subsequent submucosal maturation within limited time frames, which may be more apparent when using quantitative models to estimate outcomes. Third, the utilization of the organism's endogenous regeneration abilities may enhance the creation of bile duct substitutes. We are convinced that an interdisciplinary approach, including quantitative methods, machine learning, and deep retrospective analysis of the causes that led to success and failure in studies on the creation of bile duct substitutes, holds great value. Additionally, more attention should be directed towards the balance of epithelialization and submucosal maturation rates, as well as induced angiogenesis. These ideas deserve further investigation to pave the way for bile duct restoration with physiologically relevant outcomes.

Key Words: Bile duct alternative; Bile duct substitute; Regenerative medicine; Regenerative surgery; Theoretical surgery; Quantitative human physiology

Klabukov ID, Baranovskii DS, Shegay P, Kaprin A. Pitfalls and promises of bile duct alternatives: There are plenty of room in the regenerative surgery. *World J Gastroenterol* 2023; In press

Core Tip: Progress towards the development of clinically applicable bile duct substitutes can be achieved by applying an interdisciplinary approach. This approach should include the utilization of quantitative mathematical methods, principles of cross-tissue interactions for epithelial and submucosal tissues, as well as deep retrospective data analysis of the causes of success and failure in studies on the creation of bile duct substitutes.

TO THE EDITOR

We read with great interest the paper by Miyazawa *et al*[1], who analyzed the drawbacks and advantages of various alternatives for bile ducts. The authors described the current approaches for substituting the bile duct and acknowledged that a suitable graft has not yet been developed due to limited understanding of the mechanisms involved in the healing and regeneration of bile duct tissue. They are convinced that the use of bioabsorbable materials may facilitate the creation of bile duct substitutes in the future.

The authors have fairly mentioned that there is a 100-year history of attempts to create satisfactory bile duct substitutes[2]. However, despite significant advancements in material and life sciences, the development of engineered bile ducts has not been successful. None of the grafts currently available are reliable enough for use in clinical practice. Additionally, due to the variant anatomy of bile ducts (Figure 1A)[3,4], it is nearly impossible to completely prevent iatrogenic injuries.

One of the most valuable features of the paper by Miyazawa *et al*[1] is the systematization and analysis of the early attempts to create bile duct alternatives, as application of a systematic approach. The authors traced the history of reconstructive hepatobiliary surgery since the 1880s and discussed many intriguing studies. However, we noticed that the causes of negative or positive results are not usually analyzed or systematized in these studies. For example, in the study by Doillon *et al*, it was shown that pre-exposure of a venous graft in glycerol improves surgical outcomes[5], but the

fundamental reasons for such improvement were not investigated in this study, as well as in many other papers.

First, we want to emphasize that the analysis of the causes of negative and positive results is just as important as the results themselves. Additionally, studies that describe the unsuccessful use of rubber tubes[6], polyvinyl chloride[7], silastic[8], lyophilized and siliconized dura mater[9] in both humans and animals are valuable as they shed light on the various causes of postoperative surprises. We believe that a systematic analysis of the factors that contribute to failure or success in creating bile duct substitutes could help develop more effective approaches. It is important to note that such a systematic review has never been conducted before.

Secondly, quantitative methods of analysis can also highlight interesting patterns. Specifically, the studies reviewed by the authors revealed the limitations of bile duct epithelialization, which was found to be approximately 3 cm long and not more than 1-2 mm per week[10-12]. Additionally, the required time for submucosal maturation was estimated to be around 6-12 mo[10,13]. These findings provide support for the hypothesis that there are several deterministic mechanisms of bile duct regeneration that have yet to be discovered and completely understood. Furthermore, this suggests that the regeneration of the bile duct is delicately balanced between epithelialization and subsequent submucosal maturation within limited time frames (Figure 1B).

Thirdly, the utilization of the organism's endogenous regeneration abilities may enhance the effectiveness of bile duct substitutes. Cross-tissue interactions play a crucial role in the process of regeneration, as they determine the normal and pathological proliferation and maturation of tissues[14]. Moreover, in interconnected tissues, not only interactions but also division of labor and competition between different tissues become relevant[15]. This phenomenon has gained significant importance, particularly in relation to the biliary microbiota's role in inflammatory diseases of the biliary tract[16]. Therefore, the correct surgical approach with incompatible tissues, or the reconstruction of biliary tissues with incompatible materials, may lead to the development of chronic disorders and require additional supplementation. For example, some methods that have been

underestimated include the stimulation of not only blood vessel growth but also lymphatic vessel growth in the interstitium, as well as the specific chemotaxis of mesenchymal stromal cells to the site of injury (Figure 1C).

Miyazawa *et al*[1] have demonstrated a connection between vascularization/angiogenesis and the maturation of biliary glands, as well as the stabilization of inflammation[17]. Considering the recently discovered crucial role played by vascular endothelial growth factor in biliary tree development and cell cycle regulation[18], inducing angiogenesis could be a promising avenue for future research. It is worth noting that the use of grafts may yield varying outcomes, mainly due to differences in their structure, immunogenicity, and vascular density, regardless of whether they are autologous or allogeneic. Therefore, the mechanical (rheological) and cyto compatible properties of the substitute material are important (Figure 1D).

The functional and biomimetic properties of the bile duct substitute are expected to promote the growth of resident cells and facilitate tissue regeneration[19]. However, significant advancements in regenerative medicine necessitate innovative ideas from interdisciplinary fields. The application of mathematical logic to human physiology has the potential to accelerate progress in tissue engineering[20]. For example, the phase space method, well known in physics, can provide new insights into physiological relevance in bioengineering[21]. This promising and novel concept relies on the application of mathematical logic and machine learning to forecast surgical outcomes, commonly referred to as theoretical surgery[22].

We assume that the views of the surgeon and the biophysicist on the same facts and problems differ, particularly in terms of abstract concepts. This highlights the necessity for collaborative work among specialists from various fields (Table 1). We firmly believe that the integration of quantitative methods and retrospective analysis in bioengineering will open up new avenues for developing models of inter-tissue interaction, ultimately yielding groundbreaking outcomes in bile duct engineering.

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