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Research review

Growth factors and gastrointestinal anastomotic healing

Emile Rijcken, MD,[a,b,*] *Larissa Sachs, MD,*[a,b] *Thomas Fuchs, MD,*[b,c] *Hans-Ullrich Spiegel, MD,*[b] *and Philipp-Alexander Neumann, MD*[a,b]

[a] *Department of General and Visceral Surgery, Muenster University Hospital, Germany*
[b] *Department of Surgical Research, Muenster University Hospital, Germany*
[c] *Department of Trauma, Hand and Reconstructive Surgery, Muenster University Hospital, Germany*

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ABSTRACT

Background: Failure of anastomotic healing in the gastrointestinal tract is a major source of surgery-related morbidity, repeated surgical procedures, and impaired quality of life. Growth factors have been shown to be involved in healing processes in various tissues including the gastrointestinal tract. This opens the perspective to use growth factors therapeutically to support impaired anastomotic healing. The aim of the present study was to review the particular role of several growth factors in different phases of anastomotic healing, experimental approaches of growth factor application, and to discuss possibilities and limitations of growth factor–directed interventions in gastrointestinal surgery.

Materials and methods: A PubMed search was performed to examine the potential role of fibroblast growth factor, epidermal growth factor, heparin binding EGF-like growth factor, transforming growth factor β, insulin-like growth factor I, vascular endothelial growth factor, and platelet-derived growth factor during anastomotic healing.

Results: Growth factors show beneficial effects on a broad range of cell types and regulate various processes during all phases of tissue healing. Despite extensive research in the field of growth factors, additional evidence is needed before translating into a clinical setting.

Conclusions: Future research should focus on adequate sustained but limited drug delivery. Undesired side effects, such as formation of strictures, development of peritoneal adhesions, and potential induction of malignancies, have to be reflected. Although growth factor application is currently far from clinical routine in gastrointestinal surgery, it might find application in selected patients at risk for impaired anastomotic healing, such as patients with long-time steroid therapy, immunosuppressives, inflammatory disorders, sepsis, hemodynamic shock, malnutrition, or neoadjuvant radiochemotherapy.

* *Corresponding author*. Department of General and Visceral Surgery, Muenster University Hospital, Albert-Schweitzer-Campus 1, Building Waldeyerstr. 1, 48149 Muenster, Germany. Tel.: +49 251 83 56310; fax: +49 251 83 52400.
E-mail address: rijcken@uni-muenster.de (E. Rijcken).
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1. Introduction

Anastomotic leakage represents a major complication in gastrointestinal surgery with high impact on oncologic outcomes, the patients' quality of life, and health economic issues. Despite great progress in the field, the rate of anastomotic leakage after colonic resections still ranges between 2.5% and 37% [1–5]. Therefore, further development of anastomotic techniques or devices that may optimize anastomotic healing has been of great interest in surgical research. Numerous recent surgical publications have investigated anastomotic techniques [6], factors negatively influencing the healing process [7–9], or experimentally analyzed anastomotic healing [10,11]. In general, tension free suturing and excellent blood perfusion lead to reliable results. However, in pathologic conditions as systemic or severe local inflammation or after radiation or ischemia, the healing process can be impaired. Failure to resolve the initial inflammatory response can lead to anastomotic leakage or development of fistula, whereas uncontrolled collagen accumulation leads to excess scarring and stenosis.

Physiological anastomotic healing proceeds *via* an overlapping pattern of events that can generally be divided into three classic stages of wound repair: an exudative phase, a proliferative phase, and a reparative phase (Table 1) [9]. Beside others, growth factors have been described to play a significant role in this complex concert of tissue regeneration and wound healing. In this review, we summarize a selection of endogenous growth factors and highlight their potential therapeutic application in the distinct phases of intestinal anastomotic healing and their clinical relevance. Focus is specifically laid on those growth factors, in particular, for which results from functional *in vivo* studies on anastomotic healing are available (Table 2).

1.1. *Growth factor–derived therapy in the different phases of anastomotic healing*

In the exudative phase, immediately after tissue damage adhesion and aggregation of circulating platelets cause the release of a wide variety of molecular mediators, such as transforming growth factor β (TGF-β), vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF) (Fig. 1). Macrophages stimulated by PDGF in turn produce TGF-β, and PDGF also increases the expression of VEGF and insulin-like growth factor I (IGF-I). Direct application of PDGF in intestinal anastomotic healing has not been reported so far. However, trapidil, a triazolopyrimidine derivative originally used as a vasodilator in coronary heart disease, has been shown to act as a competitive PDGF inhibitor [27]. Repeated postoperative intravenous (i.v.) application of this drug in rats was not able to affect bursting pressure or hydroxyproline levels—used as measures for anastomotic strength—after 7 d of anastomotic healing. However, negative effects of corticosteroid use could be partly reversed by the PDGF antagonist in this model [27].

Within the 2nd to the 14th postoperative day definite wound closure begins. This proliferative phase is characterized by cellular proliferation and migration of different cell types that finally lead to reproduction of extracellular matrix, angiogenesis, and re-epithelialization (Fig. 2). Although keratinocyte growth factor (KGF) has been mainly investigated in context of dermal wound healing, intraperitoneal (i.p.) administration of KGF has been shown to promote colonic anastomotic healing in healthy rats through increased mucosal cell proliferation. After KGF administration, bursting pressures were already significantly increased on the second and fourth day after surgery [25,26]. Neoangiogenesis plays a central role in the anastomotic healing process. The most important growth factor regulators of angiogenesis are VEGF and basic fibroblast growth factor (bFGF). VEGF stimulates endothelial cell proliferation and mediates activity of the nitric oxide synthase in endothelial cells. Although its main function is stimulation of angiogenesis, VEGF also exerts nonangiogenic effects, such as stimulation of keratinocyte and fibroblast migration [28]. It induces the ingrowth of new blood vessels into the wounded area, thus in various studies on anastomotic healing, immunohistochemical or molecular VEGF detection is used as a marker for the formation of new vessels. In rabbits, intramuscular injection of VEGF-A adjacent to the suture line in colonic wounds during surgery resulted in increased bursting pressures on day 4 (but not on days 3 and 7), accompanied by increased hydroxyproline concentrations on day 4 after administration [12]. On VEGF treatment, histologic and microangiographic analysis revealed significantly higher submucosal capillary counts, and also significantly higher inflammatory cell infiltration and fibroblast proliferation compared with saline-treated controls [12]. However, treatment with bevacizumab, a recombinant humanized immunoglobulin G1 antibody that binds VEGF-A and is widely used in clinical therapy of advanced colorectal cancer, did not negatively affect anastomotic healing in the colon of rats [29]. On the contrary, anastomotic healing after esophagogastrostomy in opossums was positively influenced by VEGF gene therapy: perianastomotic submucosal injection of a plasmid construct carrying a *rhVEGF165* fusion gene resulted in increased

Table 1 – Phases of intestinal anastomotic healing.

Phase	Duration (d)	Dominating cell type	Action	Function
Exudative—inflammatory	1–4	Platelets, neutrophils, macrophages, fibroblasts	Coagulation, inflammation, edema, collagenolysis	Provisional wound closure, protection, debridement
Proliferative	2–14	Fibroblasts, smooth muscle cells, macrophages, lymphocytes	Collagen synthesis, angiogenesis, re-epithelialization	Wound stability, definitive wound closure, production of the ECM
Reparative—remodeling	14–180	Fibroblasts, lymphocytes	Remodeling, reorganization	Maturation