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Cytokines of the Wound Process and Local Immunocorrection in Chronic Paraproctitis in Adolescents

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Abstract This comprehensive literature review explores the role of cytokines and local immunocorrection in the management of chronic paraproctitis in adolescents. Chronic paraproctitis, characterized by persistent inflammation and infection of perianal tissues, poses significant discomfort and challenges in treatment, especially in the adolescent population. The review delves into the complex wound healing process, highlighting the critical role of cytokines in each stage: hemostasis, inflammation, proliferation, and remodeling. It emphasizes the imbalance of cytokine production in chronic paraproctitis, where an excess of pro-inflammatory cytokines and a deficiency in anti-inflammatory ones lead to persistent tissue damage and inflammation. The paper examines various cytokines, including TNF-alpha and IL-6, for their roles in the pathogenesis of chronic paraproctitis and their potential as therapeutic targets. The effectiveness of local cytokines, immunomodulatory drugs, surgical interventions, and novel strategies involving bioactive compounds in modulating the immune response and promoting tissue repair is analyzed. Special attention is given to local immunocorrection techniques, which have shown promise in alleviating symptoms and enhancing wound healing. This review advocates for a multi-faceted approach to treat chronic paraproctitis in adolescents, combining local cytokine therapy, immunomodulatory drugs, and surgical interventions. It underscores the need for further research to optimize these treatments, ensuring their efficacy, safety, and long-term outcomes. By advancing our understanding of cytokines and their role in immunocorrection, this paper aims to improve treatment strategies and quality of life for adolescents suffering from chronic paraproctitis.

Keywords Cytokines, Immunocorrection, Paraproctitis, Immunomodulation, Regeneration

1. Introduction

Chronic paraproctitis is a chronic inflammation and infection of the tissues surrounding the rectum and anus, especially the anal glands. It is a persistent or recurrent condition that primarily affects adolescents, causing significant discomfort and disruption of daily activities. This condition is characterized by symptoms such as perianal pain, swelling, discharge and in some cases abscess formation. The incidence of chronic paraproctitis in adolescents has been increasing in recent years, requiring further investigation into its underlying causes and the development of effective treatment strategies.

The wound healing process is a very complex and dynamic biological cascade involving a number of intricate cellular and molecular processes. Among these events, cytokines play a central role in regulating various aspects of the healing process. Cytokines are a group of small proteins secreted by various cell types, including immune cells, epithelial cells, and fibroblasts. These signaling molecules act as mediators to control inflammation, immune response, cell proliferation, and tissue remodeling [12]. In the context of wound healing, understanding the role and functions of cytokines is important as they help to maintain a delicate balance between pro-inflammatory and anti-inflammatory responses, ultimately affecting the overall healing outcome [17]. Cytokines are recognized as key regulators of the wound healing process, influencing various stages such as coagulation, inflammation, proliferation and remodeling of damaged tissues. In chronic paraproctitis, impaired wound healing mechanisms may contribute to the persistence and recurrence of the disease [16]. By studying the cytokines involved in this process, we can gain valuable information about the mechanisms underlying the development and persistence of chronic paraproctitis in adolescents.

This research paper will provide a comprehensive review of the role of cytokines in wound healing, focusing on their

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importance in chronic paraproctitis in adolescents. It reviews the existing literature emphasizing the role of cytokines in the control of inflammation, modulation of immune response, cell proliferation and tissue remodeling. The review also considers clinical studies investigating the role of cytokines in chronic paraproctitis in adolescents. The aim is to elucidate the mechanisms by which cytokines influence the development and persistence of chronic paraproctitis and to highlight potential therapeutic interventions. The article also emphasizes the importance of local immunocorrection as a treatment option for chronic paraproctitis, as understanding the immunological aspects of this condition has the potential to modulate cytokine expression and activity, contributing to improved wound healing and symptom resolution. The review also identifies gaps in current knowledge and suggests areas of future research that will enhance our understanding of chronic paraproctitis and develop more effective treatment strategies.

2. Materials and Methods

Literature Search Strategy:

Databases Searched: The review focused on comprehensive searches in major databases including PubMed, EBSCO, Web of Science, and Science Direct.

Search Terms: A combination of keywords was used, such as "chronic paraproctitis", "adolescents", "cytokines", "wound healing", "TNF-alpha", "IL-6", and "immunocorrection". Boolean operators (AND, OR) were used to refine the search.

Time Frame: Studies published between 2000 and 2023 were considered, to include the most recent and relevant information.

Inclusion and Exclusion Criteria:

Inclusion Criteria: Studies were included if they were (a) peer-reviewed articles, (b) focused on cytokines in wound healing and chronic paraproctitis, (c) involved adolescent populations, and (d) discussed immunocorrection strategies.

Exclusion Criteria: Articles were excluded if they were (a) not in English, (b) reviews or meta-analyses, (c) lacking relevance to the core topics of cytokines and chronic paraproctitis in adolescents, or (d) focused on other age groups.

Data Extraction:

For each selected study, key data were extracted, including study design, participant demographics, types of cytokines studied, methods of immunocorrection, and main findings.

Quality Assessment:

The quality of each study was assessed using standardized checklists relevant to the study design (e.g., randomized controlled trials, cohort studies). This was to ensure the reliability and validity of the included studies.

Data Synthesis and Analysis:

A narrative synthesis approach was used to analyze and combine findings from the selected studies. This involved grouping studies based on similarities in their objectives, methodologies, and outcomes.

The review particularly focused on identifying patterns and discrepancies among the studies regarding the role of cytokines in chronic paraproctitis and the effectiveness of various immunocorrection strategies.

Ethical Considerations:

Given that this is a literature review, no primary data collection was involved, and therefore ethical approval was not required. However, the review adhered to ethical standards of scientific reporting and citation.

Limitations of the Review:

The review acknowledges potential limitations, such as publication bias, the exclusion of non-English articles, and the variability in the quality of the included studies.

Review Update Plan:

Considering the evolving nature of the field, an update of the review is planned every five years to incorporate the latest research and developments.

3. Overview of the Wound Healing Process

The wound healing process is a complex and dynamic series of events that can be divided into several distinct stages: hemostasis, inflammation, proliferation, and remodeling. Each stage is characterized by specific cellular activities and biochemical processes, with cytokines playing a pivotal role throughout.

Hemostasis: The first stage of wound healing, hemostasis, involves the rapid formation of blood clots to stop bleeding. When tissue is damaged, platelets aggregate at the injury site, releasing various factors, including cytokines, to initiate the clotting process. This stage is crucial for preventing excessive blood loss and creating a matrix for cellular migration necessary for subsequent stages of healing.

Inflammation: Immediately following injury, the inflammation stage begins, characterized by the recruitment of immune cells to the wound site. Key cytokines, such as interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-alpha), are instrumental in initiating this inflammatory response. During this phase, immune cells not only clear debris and pathogens but also release chemical signals that lay the groundwork for tissue repair and regeneration.

Proliferation: This stage is marked by the migration and proliferation of various cell types essential for wound healing. Fibroblasts, which play a critical role in this stage, migrate to the wound site and begin synthesizing extracellular matrix components like collagen, crucial for repairing damaged tissue. Concurrently, endothelial cells facilitate angiogenesis—the formation of new blood vessels — to supply the regenerating tissue with necessary nutrients and oxygen.

Remodeling: In the final stage, the newly formed tissue undergoes maturation and gains structural strength. The remodeling phase involves the reorganization of the extracellular matrix and gradual replacement of excessive scar tissue with functional tissue. This process, which can span months to years, is regulated by cytokines such as transforming growth factor-beta (TGF-beta). These cytokines play a significant role in balancing scar formation and tissue regeneration.

With a clear understanding of the stages of wound healing, it is essential to delve into the role of cytokines. Many cytokines, along with other immune mediators, are intricately involved in the wound healing process, particularly in conditions like chronic paraproctitis. These cytokines not only regulate the various stages of healing but also represent potential therapeutic targets for enhancing wound repair and reducing complications. The subsequent sections will explore the specific roles and therapeutic implications of cytokines in the context of wound healing in chronic paraproctitis.

4. The Role of Cytokines

The pathogenesis of chronic paraproctitis is based on the imbalance of cytokine production and impaired regulation of the immune response. Immunological studies have shown that chronic paraproctitis is characterized by an abnormal cytokine profile with hyperproduction of proinflammatory cytokines and decreased presence of anti-inflammatory cytokines. This imbalance leads to chronic inflammation and tissue damage in the affected area [11]. Let us start with one of the major cytokines Tumor necrosis factor-alpha (TNF-alpha). Tumor necrosis factor-alpha (TNF-alpha) is a pro-inflammatory cytokine that plays a crucial role in immune response and inflammation. It is produced by various immune cells including macrophages, monocytes and T cells [10]. In chronic paraproctitis, TNF-alpha is thought to be involved in the pathogenesis of the disease. Elevated levels of TNF-alpha were observed in the affected tissues of chronic paraproctitis patients. TNF-alpha induces the release of other pro-inflammatory mediators and activates immune cells, leading to inflammation and tissue damage observed in this disease [6]. TNF-alpha is also known to promote angiogenesis (formation of new blood vessels) and tissue remodeling, which may contribute to the chronicity of the disease. It can also enhance the recruitment of immune cells to the site of inflammation, further exacerbating the immune response [7,9,12]. Targeting TNF-alpha has proven to be an effective therapeutic strategy for a variety of inflammatory diseases, including conditions such as rheumatoid arthritis and inflammatory bowel disease. In inflammatory bowel diseases, anti-TNF-alpha drugs such as infliximab and adalimumab have shown promising results in reducing inflammation, improving symptoms, and promoting healing of affected tissues [1]. However, two decades after their introduction, questions still remain about their use, including timing, dosing, monitoring, and issues related to loss of response such as risk factors, biomarkers, mechanism, and prevention and treatment strategies. Thus before using TNF targeting therapy the patient should be carefully studied as there are other therapies targeting chronic paraproctitis.

Also one of the important cytokines in chronic paraproctitis is IL-6. Interleukin-6 (IL-6): IL-6 is a multifunctional cytokine involved in various immune responses [3]. Although the exact etiology of chronic paraproctitis remains uncertain, increasing evidence suggests that dysregulation of the immune response, especially involving pro-inflammatory cytokines, plays a crucial role. IL-6, a multifunctional cytokine, has attracted attention due to its involvement in chronic inflammation and modulation of various immune processes. IL-6 is involved in the recruitment and activation of inflammatory cells, leading to local tissue damage in chronic paraproctitis. By promoting the secretion of other pro-inflammatory cytokines, IL-6 enhances the inflammatory response, contributing to the persistence of tissue destruction and exacerbation of symptoms [13]. Also, IL-6 overproduction is associated with fibrotic changes and tissue remodeling in chronic paraproctitis. It promotes the differentiation of fibroblasts into myofibroblasts, which play a key role in the production of extracellular matrix proteins and collagen deposition, contributing to fibrosis and scarring leading to worsening treatment of paraproctitis [15]. Also the most important function of IL-6 it plays a crucial role in the regulation of immune responses and the balance between pro-inflammatory and anti-inflammatory cytokines. Disruption of the regulation of IL-6 production and signaling can upset this balance, leading to an aberrant immune response in chronic paraproctitis. It is thus thought to contribute to ongoing inflammation by promoting the recruitment and activation of immune cells and enhancing tissue damage. Given the significant involvement of IL-6 in the pathogenesis of chronic paraproctitis, targeting IL-6 as a therapeutic strategy has received particular attention. Several approaches have been explored, including blockade of the IL-6 receptor and inhibition of IL-6 production or signaling. Clinical trials evaluating the efficacy and safety of IL-6-targeted therapy in chronic paraproctitis are ongoing, offering hope for improved treatment of this condition. Thus it can be concluded that the role of IL-6 in chronic paraproctitis is complex and involves multiple mechanisms contributing to disease progression. Understanding the specific role of IL-6 in the pathophysiology of chronic paraproctitis may pave the way for the development of new targeted therapies to alleviate symptoms and improve patient outcomes. Further studies are needed to elucidate the precise mechanisms underlying IL-6 involvement and optimize therapeutic strategies.

5. Immunocorrection in Chronic Paraproctitis

Chronic paraproctitis is a complex inflammatory condition

affecting the perianal area, often seen in adolescents. This debilitating condition often results in persistent pain, discomfort and frequent recurrences, significantly affecting the quality of life of those affected. Traditional approaches such as antibiotics, drainage procedures and surgical interventions have limitations in achieving long-term remission and tissue healing. Hence, the investigation of local immunocorrection as an alternative therapeutic strategy holds tremendous promise. The principles of topical immunocorrection include rebalancing the immune response by reducing pro-inflammatory cytokines, increasing anti-inflammatory cytokines, and restoring immune homeostasis. By acting on the immune affected area of the body, local immunocorrection aims to alleviate inflammation, repair tissues and prevent disease progression [2]. Also, local immunocorrection offers a targeted and effective treatment approach to modulate the immune response, especially in the perianal tissues. Using this targeted strategy, topical immunocorrection can improve symptoms, prevent disease progression, and improve the overall well-being of adolescent patients [5,6]. Topical application of cytokines such as interleukin-10 (IL-10) has shown promising results in the immunocorrection of chronic paraproctitis in adolescents. IL-10 is widely recognized for its potent anti-inflammatory properties and its ability to inhibit pro-inflammatory cytokines, thereby reducing tissue inflammation. Studies have shown that topical application of IL-10 can alleviate symptoms, accelerate wound healing, and promote tissue repair in affected individuals. However, maximizing the immunocorregulatory effect requires further research on the optimal dosage, frequency, and duration of cytokine application [9]. Immunomodulatory drugs such as corticosteroids or immunosuppressants have been studied as potential treatment options for chronic paraproctitis in adolescents. These drugs aim to modulate the immune response by reducing inflammation and inhibiting immune cell activation. Topical application of corticosteroids or suppositories, has shown promising results in reducing pain, inflammation and fistula formation [19]. However, the long-term safety and potential side effects of these drugs require careful consideration, especially in adolescents. Also surgical interventions play a crucial role in local immunocorrection of chronic paraproctitis in adolescents. Procedures such as fistulotomy, fistulectomy, or drainage aim to remove infected tissue, alleviate inflammation, and accelerate wound healing. By eliminating fistulas or abscesses, surgical interventions can effectively reset the local immune response and restore tissue stability [18]. A comprehensive evaluation of surgical outcomes and their impact on immunocorrection in adolescents is necessary for clinical decision making. Advances in local immunocorrection have allowed the introduction of innovative methods for the treatment of chronic paraproctitis in adolescents. These include the use of bioactive compounds such as growth factors, stem cells, and regenerative biomaterials to accelerate tissue regeneration and modulate the immune response. The new approaches have great potential in promoting immunocorrection, wound healing, and tissue repair, showing promising results in preclinical and early clinical trials [20]. Topical immunocorrection holds great promise as a targeted therapeutic approach in adolescents with chronic paraproctitis. By focusing on rebalancing the immune response and promoting tissue repair, this treatment modality may significantly improve the long-term outcomes and quality of life of affected individuals. Further scientific and clinical studies are needed to establish its efficacy, safety, and optimal use in the treatment of chronic paraproctitis in adolescents.

6. Conclusions

In conclusion, the aim of this research work was to study the mechanisms of regulation of wound healing by immunocytokines in adolescents with chronic paraproctitis and the use of effective methods of local immunocorrection. We studied the use of local cytokines, immunomodulatory drugs, surgical interventions and new approaches using biologically active compounds. Each method has proven effective in modulating the immune response, reducing inflammation, and promoting tissue repair.

The use of topical cytokines such as interleukin-10 (IL-10) has demonstrated efficacy in reducing inflammation and accelerating healing of chronic paraproctitis. Immunomodulatory drugs such as corticosteroids and immunosuppressants have also demonstrated the potential to control the immune response and reduce inflammation. Surgical interventions such as fistulotomy or drainage procedures have been successful in eliminating infection and accelerating wound healing. New approaches using bioactive compounds such as growth factors and stem cell therapy promise to improve immunocorrection and tissue regeneration [9].

The results presented in this review have important implications for the management of chronic paraproctitis in adolescents. By understanding and applying local immunocorrection techniques, health care providers can potentially alleviate symptoms, promote wound healing, and improve the quality of life of affected individuals.

The use of topical cytokines, alone or in combination with other therapies, offers a non-invasive option to modulate the immune response and reduce inflammation in chronic paraproctitis. This approach may help restore tissue stability and reduce symptom recurrence. Immunomodulatory drugs, when used judiciously, may also play a role in controlling the immune response and reducing inflammation, especially when local cytokines may be insufficient. Surgical interventions remain a critical component of the treatment of chronic paraproctitis. By eliminating infection and establishing proper drainage, these procedures can promote wound healing and prevent further complications. New approaches utilizing bioactive compounds hold promise to improve immunocorrection and tissue regeneration, potentially providing more targeted and effective approaches to the treatment of chronic paraproctitis. Despite the promising

results observed with cytokines and local immunocorrection techniques, further research is needed to optimize their efficacy, safety, and long-term outcomes in adolescent chronic paraproctitis.

Future studies should aim to determine the optimal dosage, frequency, and duration of cytokine administration to maximize their immunocorrective effects while minimizing potential side effects. In addition, rigorous studies are needed to establish the long-term safety and efficacy of immunomodulatory drugs. Studies comparing different surgical interventions and their outcomes in chronic paraproctitis are needed to provide evidence-based recommendations for their use. Moreover, further investigation of novel approaches involving bioactive compounds, such as growth factors and stem cell therapy, is critical to determine their potential benefits and limitations in the treatment of chronic paraproctitis. These approaches may hold the key to more targeted and effective immunocorrection, thereby improving patient outcomes.

Thus, local immunocorrection techniques offer promising avenues for the treatment of chronic paraproctitis in adolescents. Locally acting cytokines, immunomodulatory drugs, surgical interventions and new approaches using bioactive compounds have demonstrated potential in modulating the immune response, reducing inflammation and promoting tissue repair. However, further research is needed to optimize their use, ensure patient safety, and improve long-term outcomes. By continuing to explore the role of cytokines and local immunocorrection, we may be able to advance the field and offer better treatment options for adolescents with chronic paraproctitis.

REFERENCES

[1] S. O. Adegbola, K. Sahnan, J. Warusavitarne, A. Hart, and P. Tozer, “Anti-TNF Therapy in Crohn’s Disease,” Int J Mol Sci, vol. 19, no. 8, p. 2244, Jul. 2018, doi: 10.3390/ijms19082244.

[2] L. Chen et al., “Inflammatory responses and inflammation-associated diseases in organs,” Oncotarget, vol. 9, no. 6, pp. 7204–7218, Jan. 2018, doi: 10.18632/oncotarget.23208.

[3] Z. Culig and M. Puhr, “Interleukin-6: a multifunctional targetable cytokine in human prostate cancer,” Mol Cell Endocrinol, vol. 360, no. 1–2, pp. 52–58, Sep. 2012, doi: 10.1016/j.mce.2011.05.033.

[4] R. H. Dosh, N. Jordan-Mahy, C. Sammon, and C. Le Maitre, “Interleukin 1 is a key driver of inflammatory bowel disease-demonstration in a murine IL-1Ra knockout model,” Oncotarget, vol. 10, no. 37, pp. 3559–3575, May 2019, doi: 10.18632/oncotarget.26894.

[5] C. M. Dumont, J. Park, and L. D. Shea, “Controlled release strategies for modulating immune responses to promote tissue regeneration,” J Control Release, vol. 219, pp. 155–166, Dec. 2015, doi: 10.1016/j.jconrel.2015.08.014.

[6] S. Fujino et al., “Increased expression of interleukin 17 in inflammatory bowel disease,” Gut, vol. 52, no. 1, pp. 65–70, Jan. 2003, doi: 10.1136/gut.52.1.65.

[7] B. Gareb, A. T. Otten, H. W. Frijlink, G. Dijkstra, and J. G. W. Kosterink, “Review: Local Tumor Necrosis Factor-α Inhibition in Inflammatory Bowel Disease,” Pharmaceutics, vol. 12, no. 6, p. 539, Jun. 2020, doi: 10.3390/pharmaceutics12060539.

[8] A. C. de O. Gonzalez, T. F. Costa, Z. de A. Andrade, and A. R. A. P. Medrado, “Wound healing - A literature review,” An Bras Dermatol, vol. 91, no. 5, pp. 614–620, 2016, doi: 10.1590/abd1806-4841.20164741.

[9] R. Ito et al., “Interferon-gamma is causatively involved in experimental inflammatory bowel disease in mice,” Clin Exp Immunol, vol. 146, no. 2, pp. 330–338, Nov. 2006, doi: 10.1111/j.1365-2249.2006.03214.x.

[10] S. S. Iyer and G. Cheng, “Role of interleukin 10 transcriptional regulation in inflammation and autoimmune disease,” Crit Rev Immunol, vol. 32, no. 1, pp. 23–63, 2012, doi: 10.1615/critrevimmunol.v32.i1.30.

[11] D.-I. Jang et al., “The Role of Tumor Necrosis Factor Alpha (TNF-α) in Autoimmune Disease and Current TNF-α Inhibitors in Therapeutics,” Int J Mol Sci, vol. 22, no. 5, p. 2719, Mar. 2021, doi: 10.3390/ijms22052719.

[12] I. V. Joffe and S. N. Usachev, “[IMMUNOHISTOCHEMICAL AND CYTOLOGICAL ASSESSMENT OF LOCAL INFLAMMATORY REACTION IN THE EARLY POSTOPERATIVE PERIOD IN PATIENTS UNDERGOING SURGERY FOR COMPLEX FORMS OF ACUTE PARAPROCTITIS],” Klin Khir, no. 6, pp. 25–28, Jun. 2015.

[13] S. Kany, J. T. Vollrath, and B. Relja, “Cytokines in Inflammatory Disease,” Int J Mol Sci, vol. 20, no. 23, p. 6008, Nov. 2019, doi: 10.3390/ijms20236008.

[14] K. A. Kuhn, N. A. Manieri, T.-C. Liu, and T. S. Stappenbeck, “IL-6 stimulates intestinal epithelial proliferation and repair after injury,” PLoS One, vol. 9, no. 12, p. e114195, 2014, doi: 10.1371/journal.pone.0114195.

[15] M.-C. Li and S.-H. He, “IL-10 and its related cytokines for treatment of inflammatory bowel disease,” World J Gastroenterol, vol. 10, no. 5, pp. 620–625, Mar. 2004, doi: 10.3748/wjg.v10.i5.620.

[16] Y. Li, J. Zhao, Y. Yin, K. Li, C. Zhang, and Y. Zheng, “The Role of IL-6 in Fibrotic Diseases: Molecular and Cellular Mechanisms,” Int J Biol Sci, vol. 18, no. 14, pp. 5405–5414, 2022, doi: 10.7150/ijbs.75876.

[17] F. Sanchez-Munoz, A. Dominguez-Lopez, and J.-K. Yamamoto-Furusho, “Role of cytokines in inflammatory bowel disease,” World J Gastroenterol, vol. 14, no. 27, pp. 4280–4288, Jul. 2008, doi: 10.3748/wjg.14.4280.

[18] G. S. Schultz, G. A. Chin, and L. Moldawer, “23 Principles of Wound Curative”, Accessed: Oct. 08, 2023. [Online]. Available: https://7hui5bboe4qxjg3.com/a-ridge-blank-surrounds-and-protects-bacterial-cells.

[19] H. Tabry and P. A. Farrands, “Update on anal fistulae: surgical perspectives for the gastroenterologist,” Can J Gastroenterol, vol. 25, no. 12, pp. 675–680, Dec. 2011, doi: 10.1155/2011/931316.

[20] J. K. Triantafillidis, E. Merikas, and F. Georgopoulos, “Current and emerging drugs for the treatment of

inflammatory bowel disease," Drug Des Devel Ther, vol. 5, pp. 185–210, Apr. 2011, doi: 10.2147/DDDT.S11290.

[21] S. Xu and X. Cao, "Interleukin-17 and its expanding biological functions," Cell Mol Immunol, vol. 7, no. 3, pp. 164–174, May 2010, doi: 10.1038/cmi.2010.21.