НАУКА

ANALYSIS OF POLYMORPHISM OF MATRIX METALLOPROTEINASE-2 ($C^{-1306} \rightarrow T$) AND TISSUE INHIBITORS OF METALLOPROTEINASE-2 ($G^{303} \rightarrow A$) GENES IN PATIENTS WITH ANASTOMOTIC LEAK IN HOLLOW DIGESTIVE ORGANS

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Despite the improvement of existing techniques and the development of new surgical technologies, the anastomotic leak in the hollow digestive organs is one of the most difficult complications in abdominal surgery. The incidence of such complications, according to various authors, ranges from 2-8.1% in small bowel anastomosis to 3.8-14.6% in operations on the colon [1,2]. Anastomotic leak is accompanied by mortality rate of 14-21.7% [3]; with the development of disseminated peritonitis, abdominal sepsis mortality increases up to 43-82.9% [1,4]. So far, there is no single point of view in the surgical community regarding the causes of anastomotic leak development and surgical tactics in the development of these complications. According to the literature on the subject, among the risk factors for the development of an anastomotic leak are microcirculation disruption in the anastomosis area, tissue regeneration failure, infection, increased intra-intestinal pressure, changes in the rheological properties of blood, homeostatic imbalances, etc. [1]. A separate group of risk factors includes tactical and technical errors in the formation of anastomosis [5].

Although there is no doubt about the role of regenerative processes in the formation of intestinal anastomosis [6,7], scientific publications and research at the current methodological level on this topic are not enough. An in-depth study of the mechanisms of reparative regeneration in the area of the anastomosis and possibilities of regenerative processes stimulation, adequate restoration of morpho-functional characteristics of digestive organs that have been anastomosed is necessary. In domestic and foreign sources, there are almost no publications about the role of undifferentiated dysplasia of the connective tissue (UDCT) in the development of anastomotic leak in hollow digestive organs.

Anastomosis formation is a complex molecular- and cell-mediated process aimed at restoring of the continuity of the hollow digestive organs [7]. It involves both classical processes of inflammation: alteration, exudation, proliferation, and specific reparative processes due to suture technique, suture material, the presence of infection, and other factors [8].

Given the almost unexplored role of genetic predisposition in the development of postoperative complications, namely the failure of anastomotic sutures, we set a goal to study the polymorphism of genes encoding matrix metalloproteinase-2 (MMP-2) and tissue inhibitor of matrix metalloproteinase-2 (TIMP-2). The choice of these genes was not accidental - we were guided by the main known pathophysiological mechanisms involved in the formation of the intestinal anastomosis [7].

Matrix metalloproteinases (MMPs) are a group of enzymes represented by cysteine, serine, aspartyl, and metal-dependent proteinases. They belong to Zn^{2+} - and Ca^{2+}-dependent endopeptidases, which are involved in the remodeling of connective tissue due to the destruction of its organic components at normal pH values. MMPs play a major role in the metabolism of connective tissue proteins. These enzymes are also involved in many physiological (embryonic development, morphogenesis, migration, adhesion, angiogenesis, involution, and tissue remodeling) and pathological (inflammation, malignancy, cardiovascular, pulmonary diseases, arthritis) processes. They are also able to model the activity of growth factors, cytokines, and their receptors. Enzymes from the MMPs group (MMPs -2, -3, -9) affect vascular wall permeability and angiogenesis by regulating the catabolism of extracellular matrix components and cell-matrix interactions [9]. Currently, approximately 30 different MMPs are known, which are divided into 5 groups based on substrate specificity: collagenases; gelatinases; stromelysins; membrane-bound; other matrixins not included in the above groups. The gelatinase subfamily includes 2 enzymes - gelatinase A (MMP-2) and gelatinase B (MMP-9). MMP-2,9 show a high affinity for type IV collagen, so they are sometimes called type IV collagenases. MMP-2 occupy a central position in the regulating of the balance between the processes of synthesis and proteolysis in the extracellular matrix, affect the implementation of physiological processes and pathological changes in the body [9].

The main regulators of matrix metalloproteinases are tissue inhibitors of metalloproteinases - TIMPs (TIMP-1, TIMP-2, TIMP-3, TIMP-4). All 4 groups of TIMPs can inhibit the proteolysis of latent forms of MMP and inhibit the active forms of MMP, but TIMP-1 is more active against MMP-9, and TIMP-2 shows specificity for MMP-2 [10].

Recently these enzymes, namely their expression, polymorphism of the genes that encode them, have been actively studied as diagnostic and prognostic factors in oncological diseases [11,12,13], cardiovascular pathology [14,15], ophthalmology [16], etc.

At the same time, information on the role of MMPs in the development of anastomotic leak in hollow digestive organs is almost absent. During the analysis of the literature, we found a small number of publications on the study of MMP expression in the colorectal anastomoses leak [17-19], postoperative peritonitis [20,21].

However, we have not found publications on the study of genetic polymorphism of matrix metalloproteinases and their regulators in terms of the development of anastomotic leak.

The aim - to analyze the frequency of polymorphic variants of genes MMP-2 ($C^{-1306} \rightarrow T$) and TIMP-2 ($G^{303} \rightarrow A$) in patients with anastomotic leak in hollow digestive organs.

Material and methods. A retro- and prospective trial was based on data on 61 patients, who were treated at the Shalimov National Institute of Surgery and Transplantology. 17 of 61 patients (experimental group 2) suffered anastomotic leak in hollow digestive organs, 44 of 61 patients (experimental group 1) had phenotypic signs of UDCT. For the assessment of genetic polymorphism in the population, 80 practically healthy people