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Role of the transforming Rost Factor B in the patogenesis structural remodulation of the Slice Trachy in experimental Tracheobronchitis

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Abstract

A study of transforming growth factor β1 was carried out to examine the morphological changes of the tracheal wall in a model of aseptic inflammation. By the 14th day of the experiment TGF-ß1 concentration in plasma was more than 5 times higher than in intact animals. The result of such "overproduction" of TGF-ß1 is rearrangement of tracheal mucosa towards reduction of cells of atrial epithelium, bocalytic cells, appearance of foci of fibrosis spreading to submucosa layer, significant increase in volume proportion of fibrous tissue around cartilage, vessels, glands, as compared to control group. The above suggests that increased TGF-β concentration is an important prognostic criterion for pathological fibrosis.

Keywords: transforming growth factor β1, tracheobronchitis, proliferative stage of inflammation

Introduction

Representatives of the transforming growth factor β (TGF-β) family were first described in 1978. This group of growth factors was named because of its ability to induce transformation of normal cell phenotype. [3,14,16]. TGF-β belongs to the family of dimeric polypeptides with a molecular weight of 25 kDa, which are widely present in tissues. Sources of TGF-β are predominantly monocytes and macrophages, which contain it permanently but secrete it only when activated.

In addition, other cells, such as fibroblasts, endotheliocytes, neutrophils, eosinophils, mast cells, smooth muscle cells, and cells of many types of malignancy, can also produce TGF-β [3,8,15,17]. TGF-β exists in 5 isoforms, three of which are expressed in normal mammalian tissues and are denoted as TGF-β, TGF-β2 and TGF-β3. Each isoform is encoded by a unique gene located on different chromosomes. The three isoforms of TGF-β have similar biological effects, but TGF-β1 has the most prominent expression and a significant role in inflammation, vascular and myocardial remodelling and fibrosis, so this isoform is of most interest to researchers [1,5,6,13]. Activation of the TGF-β1 gene occurs in response to tissue damage. The propeptide, or latency associated peptide (LAP), remains bound to the mature molecule by non-covalent interactions. This ensures that the mature protein molecule is a biologically inactive, latent form in which TGF-β is stored in the extracellular matrix. Activation of TGF-β occurs through cleavage of LAP propeptide involving factors such as proteases, integrins, changes in pH and reactive oxygen species. TGF-β1 has been shown to promote fibrotic processes [2,4,9]. TGF-β1, together with other cytokines such as tumour necrosis factor-β and interleukin-1(IL-1), is involved in vascular remodelling [6,16,17].

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Materials and Methods of Study

This investigation was carried out on 59 male white mongrel sexless rabbits weighing 1200-1500 g. The animals were divided into the following groups: the first control group consisted of 5 animals kept in conditions of the vivarium throughout the experiment at an ambient temperature of 22°C. The second control group consisted of 24 falsely operated animals. The experimental group consisted of 30 animals, in which the model of aseptic inflammation of the trachea was reproduced according to the method developed by us [11]. The essence of the proposed method was the damage of all layers of the anterior tracheal wall by chloroethelium which was applied through a window of constant diameter until white hoarfrost appeared on the tracheal wall. Falsely operated animals were opened to the anterior tracheal wall with a midline incision and the wound was sutured layer by layer. The studies were performed taking into account the requirements of the Declaration of Helsinki of the World Association "Ethical Principles of Scientific Research Using Experimental Animals" [10]. The concentration of TGF-beta in animal serum was determined by solid-phase enzyme immunoassay using commercial ELISA test systems manufactured by R&D Systems (USA) at 5, 7 and 14 days after modeling inflammation and false surgery. Histological preparations of the trachea were stained with hematoxylin-eosin and van Gizon macrofuchsin [12,18]. In light microscopy, inflammatory, dysregenerative (basal cell proliferation, the presence of squamous cell metaplasia and bocalytic cellular dysplasia) and fibrotic processes were evaluated.

The results were statistically processed using Biostatistica software. The significance of differences was assessed by Student's t-test.

Results of the Study and their Discussion

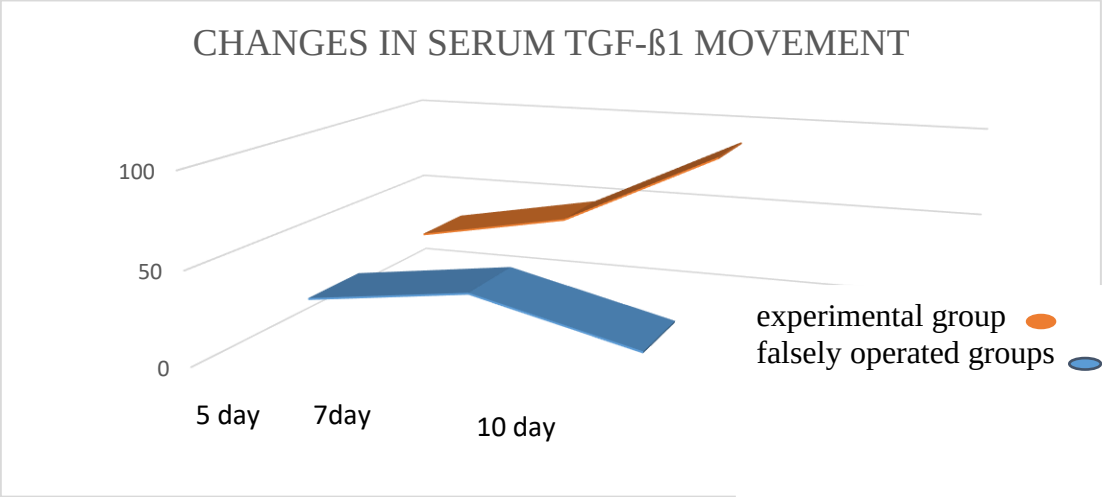
The analysis of TGF-ß1 content in blood plasma of experimental animals showed a significant increase in its concentration compared to intact animals (Table 1) in all study periods.

TGF-ß1 content in serum of animals with experimental aseptic inflammation of tracheaм.

Table 1. The analysis of TGF-ß1 content in blood plasma of experimental animals

Day	TGF- ß1 concentration experimental gr. (pg/ml)	TGF- ß1 concentration false-opaque gr. (pg/ml)
Day 5	33,67±3,82[a]	29,13±1,89 [a]
Day 7	49,37±4,81 [a]	40,44±3,08 [a]
14 day	90,54±8,35 [a,b]	20,25±2,57
Inactivated	17,04±1,18	

Note: a - Results valid compared with intact animals (p<0.05);b - the results are valid compared with those of falsely operated animals (p<0.05).

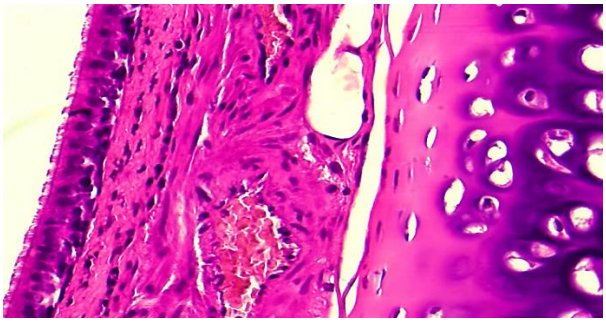


So, by day 5 after reproducing the model of aseptic tracheal inflammation the TGF-ß1 concentration excess was 97.6%, in the group of falsely operated animals the excess was 70.9%. Day 7 of the experiments was characterized by a further increase in the concentration of the investigated factor both in the experimental and falsely operated animal groups. By the final term of the studies TGF-ß1 concentration in plasma of the animals with the model of aseptic inflammation reached the maximum values - 90.54±8.35 pg/ml which is more than 5 times higher than in intact animals. Concentration of TGF-ß1 did not significantly differ from the values of the intact animals in the group of the falsely operated animals. Such increase of TGF-ß1 concentration in the group of animals with the model of aseptic inflammation unequivocally indicates the role of this factor in determining the severity of the underlying process. What morphological changes can be associated with the so-called "overproduction" of TGF-ß1. To find answers to this question, we investigated morphological changes in the tracheal wall of animals with experimental aseptic inflammation.

The study of material from intact animals showed that in the absence of experimental influences the epithelial layer of the tracheal mucosa has a normal structure typical of mammals. The trachea of intact rabbits was lined by a single-layer prismatic prismatic epithelium with a thin basal membrane. The epithelium consists of ciliated cells, which on the apical surface contain cilia, whose flickering expels mucus from the airways; bocalytic cells refer to single-celled mucus glands; low and high insertion cells, which are undifferentiated elements; endocrine cells are pyramidal and contain secretory granules with biologically active substances in the basal part. Mucosal membrane and submucosa showed loose fibrous connective tissue with single diffusely dispersed lymphocytes and histiocytes.

The material from the experimental group of animals on the 14th day after reproducing the model of aseptic inflammation showed clear morphological changes in the epithelium of the tracheal mucosa. Epithelial layer was distinguished first of all by its reduced height, epithelium border was uneven, cells were small. Focal epithelial metaplasia was detected. Re-epithelialisation of the covering epithelium in the form of hyperplasia and hyperchromasia of the cylindrical epithelium with a low content of bocalytic cells. The basal membrane is thickened in places, with foci of fibrosis extending to the submucosal layer. Proliferation of fibrocytes and fibroblasts with formation of fibrous tissue interlayers, thickening of the vascular wall due to proliferation of cellular elements. In general, the volume proportion of fibrous tissue around cartilage, vessels, and glands significantly increased as compared to the control group, while the proportion of loose fibrous connective tissue decreased. Cartilage loosening due to chondrocyte swelling (Fig. 1).

Figure 1. Cartilage loosening due to chondrocyte swelling.



Conclusion

It is known that practically all tissues of the body have a supply of cambial cells, capable of replenishing its cellular composition, which is constantly being destroyed under functional overload or under the action of phlogogenic factors. Due to a relatively low level of proliferative activity, the epithelial lining of the mucosa of the airways is considered to be a slowly renewing tissue system [2,18]. The results of these studies showed a significant increase in the concentration of transforming growth factor β1 in animals with aseptic inflammation of the trachea. A significant increase in the investigated factor occurred on the 14th day of the experiments. The positive anti-inflammatory role of TGF-β1 becomes problematic when the degree of activation of the cells producing this cytokine is no longer adequate, and the original protective mechanism is transformed into a pathological one. The result of cytokine overproduction is a rearrangement of the tracheal mucosa towards a decrease in the cells of the atrial epithelium, bocalytic cells producing mucus of liquid consistence, hyperproliferation of fibroblasts, increased synthesis of collagen and, consequently, subsequent tissue fibrosis. These are the changes we found in the morphological study of the tracheal wall on the 14th day of the experiments. This structural remodelling of the tracheal wall with a disproportionate growth of connective tissue elements disrupts the trophism of all layers of the tracheal wall, primarily the mucosa. The main cells producing TGF-β are cellular elements of connective tissue (macrophages, fibroblasts, mast cells), whose number increases with each new damage to the airways. These dynamics lead to an imbalance in the ratio of pro- and anti-inflammatory cytokines, with the development of a deficiency of the latter. Repeated inflammatory processes with damage to epithelial tissue eventually deplete the ability to reepithelialize, an inadequate healing process develops, the extracellular matrix weakens, and excessive movement of fibroblasts into the affected areas occurs. The above suggests that increased concentration of TGF-β is one of the important prognostic criteria of pathological fibrosis. In our opinion, it is these aspects of the pathogenesis of the proliferative stage of the inflammatory response that underlie the chronicity of many forms of airway pathology. Further studies of cellular and molecular mechanisms of inflammatory response formation in the airways system are likely to create prerequisites for the development of pathogenetic ways to correct the imbalance of pro- and anti-inflammatory cytokines.

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