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Review article

Advances in biomaterials for preventing tissue adhesion

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ABSTRACT

Adhesion is one of the most common postsurgical complications, occurring simultaneously as the damaged tissue heals. Accompanied by symptoms such as inflammation, pain and even dyskinesia in particular circumstances, tissue adhesion has substantially compromised the quality of life of patients. Instead of passive treatment, which involves high cost and prolonged hospital stay, active intervention to prevent the adhesion from happening has been accepted as the optimized strategy against this complication. Herein, this paper will cover not only the mechanism of adhesion forming, but also the biomaterials and medicines used in its prevention. Apart from acting as a direct barrier, biomaterials also show promising anti-adhesive bioactivity though their intrinsic physical and chemical are still not completely unveiled. Considering the diversity of human tissue organization, it is imperative that various biomaterials in combination with specific medicine could be tuned to fit the microenvironment of targeted tissues. With the illustration of different adhesion mechanism and solutions, we hope this review can become a beacon and further inspires the development of anti-adhesion biomedicines.

1. Introduction

Adhesion is caused by the interweaving of fibrin from extensive interstitial fluid leakage, being the result from various conditions such as surgical incision, trauma and other pathological situations [1]. When granular tissue rich in capillarity gradually replaces necrotic tissue, a fibrinous network forms *in situ*, which can ultimately causes fibrinous adhesion and subsequent dysfunction of the tissue. Briefly, a colloidal matrix of fibrin forms within three hours after injury, marking the starting point of granulation tissue infiltration. Fibroblasts [2] and macrophages [3] recruited to local damaged tissue, together with the fibrin matrix, form granulation tissue in one to three days. Subsequent increase in fibroblast and macrophage numbers in day four helps forming the fibrinous network. Approximately two weeks after injury, fibrous adhesion takes shape *in situ*, along with the disappearance of most cells in the network.

Strategies for preventing adhesion usually proceed from either the management of damaged tissues or the application of biomaterials. Tissue-based methods involve cutting off adhesion forming processes, specifically by alleviating the inflammation and exudation of focal tissues, restraining the deposition and clotting of fibrin and protection of wound surface from friction. As one of the main cell types responsible for of the production of fibrin and initiating tissue overgrowth, fibroblasts are also the target of anti-adhesion treatment. Suppression of these cells has also been widely explored in preclinical trials. As for biomaterial-based methods, anti-adhesion is usually achieved by taking advantage of the physical and chemical properties materials. In another words, biomaterials act as physical barriers or bioactive agents able to suppress the formation of adhesion. This article will start with a systematic review of different types of problems related with tissue adhesion that are common during clinical work, along with their corresponding mechanisms. Prevention of adhesion with various biological scaffolds, membranes and drugs will then be summarized and critically appraised in order to look towards the future development of anti-adhesion biomaterials.

2. Adhesion disease

In clinical practice, fibrous adhesion typically involves tissues such as tendon [4], dural sac [5], intestinal [6], peritoneum [7], pericardium

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and uterine. Besides normal symptoms such as pain, dyskinesia and paralysis, adhesion in specific organs such as the uterine cavity and oviducts can result in organ-specific symptoms such as menoxenia and reproductive dysfunction. Incidence of life-threatening illnesses such as ileus and cardiac failure can also be traced to adhesion in corresponding tissues. Therefore, the issue of adhesion is a major cause of severe pain and heavy economic burden globally, which prompted the development of anti-adhesion biomaterials and medicines.

2.1. Tendon adhesion

Considered to be closely associated with its healing mechanism, adhesion of tendons accounts for most problems in the motor system such as articular dyskinesia and periarthritis. Both endogenous and exogenous factors contribute to the healing of tendons. In the process of endogenous tendon healing, the stimulation of bioactive factors contained in synovia promotes proliferation and surface or internal migration of tenocytes. Exogenous healing depends on exogenous fibroblasts proliferating in the granulation tissue that grows into the defect of the damaged tendon. This mechanism tends to result in scarring during healing, which subsequently develops into fibrous adhesion and ultimately affects the contraction of the tendon [8]. An imbalance of endogenous and exogenous healing, attributed to the various locations and degree of damage to the tendon, is recognized to be responsible for adhesion. Improper postsurgical movement of the damaged tendon is also thought to be associated with enhanced exogenous healing and corresponding adhesion. During this type of healing process, an increased number of fibroblasts in the local microenvironment is observed as the result of migration from peripheral tissue to the margin of the tendon defect. This leads to vast deposition of fibrin, which causes adhesion between the tendon and peripheral tissue. Apart from that, focal inflammation contributing to increased exudation can also aggravate fibrin leakage in defect site.

As the mechanism of tendon adhesion is widely reported, several findings at the molecular level can be seen as key events. Derby et al. found a gene with increased expression at the healing site of a tendon wound and the matrix of scar tissue where inflammatory cells were infiltrating. Named as Reactive gene-1 [9], the expression product of this gene can enhance exogenous healing and aggravate adhesion. A protein named Smad3 whose overexpression can result in more severe adhesion was reported by Loiselle et al. [10] and Katzel et al. [11]. It is hypothesized that suppressing the expression of this protein can decrease the focal deposition of collagen, hence alleviating scar formation. Also, the presence of matrix metalloproteinase 9, derived from bone marrow, at healing site is reported to promote adhesion, although a specific mechanism is still under debate. Illustration of tendon adhesion is shown in Fig. 1.

2.2. Epidural adhesion

Key, Ford et al. [12] seminal work on the Anterior Source theory about the mechanism of epidural adhesion in 1948 set intraoperative damage of intervertebral disc as the reason for postsurgical adhesion of dural sac. Yet in 1974, the Posterior Source theory from LaRocca et al. [13] stated that it is the laminectomy membrane formed due to the damage of dorsal musculus sacrospinalis that results in adhesion by means of fibroblast infiltration. Recognized by most researchers as the doctrine to follow, Posterior Source theory has guided anti-adhesion clinical work and preclinical studies for decades. With the validation of a wide range of research work, Songer et al. [14] found that not only damage to the intervertebral disc and posterior longitudinal ligament but also a wounded erector spinae can become the source of scar tissue, and subsequent adhesion can produce a tractive force on the nerve root beside the dural sac. Since then, a three-dimensional theory of adhesion forming mechanisms has gradually come into shape. Inspired by the principle of this theory, a biomedical barrier between the dural sac and scar tissue may prevent the formation of adhesion. Thus, a series of studies on this “barrier” was conducted in order to reduce the post-surgical damage of nerve root due to adhesion.

Basically, epidural adhesion comes from epidural scar tissue, in which fibroblast plays a pivotal role during its formation. A number of minor reasons such as inflammation and hematoma are considered to promote adhesion by affecting fibroblast are summarized in the following. Hematoma and inflammation resulting from trauma, infection and foreign matter play important roles during the formation of epidural scar. Inflammatory mediators such as prostaglandin, leukotriene, interleukin-1 (IL-1) involved in the activation and chemotaxis of fibroblasts, promote the generation of scar tissue and subsequent adhesion. Dural hematoma can also act as mediator of scar tissue as it can be infiltrated by fibroblasts and ultimately result in the spread of adhesion into the spinal canal. Furthermore, growth factors such as transforming growth factor beta (TGF-beta), platelet derived growth factor and fibroblast growth factor released from hematoma promotes the proliferation and differentiation of fibroblasts. Therefore, inhibiting the formation of hematoma or accelerating hematoma degradation plays an important role in the prevention of epidural adhesion. Illustration of epidural adhesion is shown in Fig. 1.

2.3. Pericardial adhesion

Proceeding with the leaps of medical technology at the end of the 20th century, sophisticated techniques involved in cardiac surgery became commonplace in clinical practice. Such interventions include aortocoronary bypass surgery and valve replacement surgery, which used to be considered impossible. However, these procedures were accompanied by degeneration of implants and other complications. The rate of secondary surgery thus rose over time, which meant a larger number of cardiac surgeries and greater odds for potential vascular and pericardial injury, both of which can elicit adhesion of pericardium. Also, hematoma due to intra- or post-surgical bleeding can promote scar tissue generation. As evidenced by *in vivo* preclinical studies, damaging of interstitial tissue due to injury, infection, ischemia and hemorrhage is considered as a necessary condition for adhesion to occur [15].

As a good example of pericardial adhesion (Fig. 1), the process after pericarditis encompasses four steps. Firstly, exudation after inflammation leads to deposition of fibrin monomer within 24 h. Secondly, following the detachment of injured mesothelial cells and fibrin deposition, cellulose deposits on interstitial tissue in the following two days. Thirdly, in the up-coming week, with the infiltration of the neovascule and lymphatic tubes, fibrin in the lesion site degrades, followed by a deposition of collagen. Finally, local adhesion forms approximately two weeks after acute onset [16].

The cause of pericardial adhesion can be primarily considered as the intra-operative peeling-off of pericardial mesothelial cells and subsequent adhesion of fibrin, platelets and inflammatory cells at the site. Over-produced fibrin and fibroblast can also break the local balance and cause deposition of scar-inducing substances.

2.4. Intrauterine adhesion

First reported by Fritsch in 1894, intrauterine adhesion (IUA) refers to adhesion between the uterine muscle wall or cervical canal resulting from injury to the uterine cavity or cervical canal due to various factors [17]. A detailed depiction of IUA and a large quantity of cases have long been reported by Asheman et al. and, thus, symptoms caused by IUA are also known as Asheman Syndrome [18]. As the conclusions from a retrospective study of 2981 cases from more than 90 studies of Asheman Syndrome by Schenker and Margalioth indicates, IUA can result mainly from: (i) iatrogenic injury during pregnancy such as postpartum curettage, pregnancy termination and cesarean section; and (ii) non-pregnancy injury of the uterus such as curettage, uterus tumor rejection, cervical biopsy or polyp resection, placement of IUD and