Determining the Biological Properties of Biomaterials In Vivo

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Abstract Biocompatibility, bioinertness and biofunctionality are prerequisites was that certain materials could be used in implantation. In vivo studies of biomaterials involves the assessing of overall biocompatibility of the newly synthesized biomaterials. In contact with organism, biomaterials represent foreign bodies and organism can react in various desirable and undesirable ways. As response to biomaterials, two types of hypersensitivity reactions are common, type I and type IV. Materials that are routinely used in dentistry can give rise to hypersensitivity reactions in both sensitised patients and members of the dental team. Hypersensitivity reactions to the endovascular prostheses are among the infrequent and unpredictable reactions that may lead to local or systemic complications. After implantation biomaterials initiate a host response which begins with blood-biomaterial interactions and provisional matrix formation and continues with acute/chronic inflammation, granulation tissue emergence, foreign body reaction, development of fibrous capsule and possible fibrosis. Macrophages are cells that regulate the host response to implanted biomaterial at several levels. Evaluation of the effect of the implant includes a large number of biological parameters e.g. thickness and vascularization of fibrous capsule, the number and size of inflammatory cells, cell infiltration in implant, degenerative and necrotic changes in the surrounding tissues, cell apoptosis, proliferation and differentiation, endothelialization, biodegradation, the thrombus formation, calcification. Effects of biomaterial at the site of implantation depend on its size, shape, surface and physicochemical characteristics. Ideal result of implantation would be complete restoration of normal tissue architecture and function after healing of injuries.

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1 Introduction

The development of new biomaterials is a lengthy process that includes structural analysis, optimization, testing of biocompatibility and eventually clinical trials.

Tissue damage occurring under different circumstances (trauma, fractures, infections, tumors and the like). Balanced activity of cells the body most damaged part can independently repaired. However, with the emergence of major damage, it is necessary to support the biological potential for reparation for example in a large loss of bone tissue. The resulting damage in regenerative medicine reimbursed graft and implants example. Only in the US are carried out annually over one million compensation and repair of bone tissue (Olivier et al. 2004).

Autotransplantation represents the gold standard for compensation of damage despite many shortcomings. The biggest disadvantage of the autotransplantation is the most commonly a small number of places in the body where it is possible to take material for autotransplantation as its small amount. Alternative autotransplantation including allogeneic and xenogeneic transplant. The possibility of using allogeneic and xenogeneic transplant is limited in terms of histocompatibility and immune tolerance. Some natural [e.g. a natural source of hydroxyapatite to regenerate bone tissue are coral genus Porites (Yaszemski et al. 1996)] or artificial materials can be used as a substitute for the missing tissue. They are so far used in slightly less than 10% of cases resulting compensation (Olivier et al. 2004).

Because of many limitations in using autotransplants and allotransplants, bone tissue engineering (BTE) techniques are becoming nowadays an important alternative for bone defects repair (Li et al. 2014). In bone tissue engineering biodegradable porous scaffolds which mimic 3D structure of natural bone have been imposed as good functional solution. Their characteristics is that they can be mechanical support instead of the missing bone skeleton. Besides, their porosity allows cell growth, cell functions and behavior required for tissue regeneration, as well as vascularization as an important condition for new bone formation. Due to biodegradation ability scaffolds create a space that will be filled with new bone, and thus BTE construct replaced by natural tissue. (Hutmacher 2000). In addition to the above aforementioned properties, scaffolds which by their geometry imitate natural bone extracellular matrix (ECM), i.e. microenvironment for bone cells growth and activity, are tested (Hutmacher et al. 2007; Douglas et al. 2009).

Implantation represents the incorporation of materials into the body. The materials used for this purpose are different as, for example, metals (titanium and its alloys, cobalt–chromium–molybdenum alloy), ceramics (gypsum, hydroxyapatite, alumina, tricalcium phosphate, carbon), glass, polymers (Teflon, silastik, Ivalon). Biocompatibility, bioinertness and biofunctionality are prerequisites was that certain materials could be used in implantation.

The material is biocompatible if it is directly connected with the tissue in which it is installed and contributes to tissue reparation on site. Bioinertness of the material implies its non-toxicity on the body, as well as the exclusion of genotoxicity and the transformation of normal cells into cancer cells. Biofunctionality is reflected in the fact that the fabric retains the normal functions of the installation materials (Ignjatović et al. 2001; Najman et al. 2003, 2004; Vasiljevic et al. 2009, 2013; Jokanović et al. 2016a).

Having in mind that inorganic component of bone is mostly composed of hydroxyapatite, ceramic biomaterials, tricalcium phosphates (TCF) and hydroxyapatites (HAP) have attracted significant attention of researchers. (Ghanaati et al. 2013; Jokanović et al. 2006, 2016a, b). That is the reason why they have a great advantage in biocompatibility compared to other biomaterials. On the other side, their biofunctionality is weaker than in other biomaterials, due to high brittleness they possess. For this reason, ceramic biomaterials cannot be used to repair bone tissue when there is an interruption of continuity of bone (Ignjatović et al. 2001; Najman et al. 2003, 2004; Vasiljevic et al. 2009). There are many attempts to overcome embrittlement, as the main problem in the application of ceramic biomaterials. Disadvantages of ceramics can be at least partly corrected by using polymers such as poly-L-lactide, poly-lactide-co-glycolide, etc. (Durucan and Brown 2000; Ignjatović et al. 2001; Najman et al. 2003, 2004; Vasiljevic et al. 2009, 2013; Mitić et al. 2014). It is shown that composite scaffolds constructed of calcium phosphate and poly (lactide-co-glycolide) (PLGA) have better mechanical properties, such as compressive strength, rather than scaffold without PLGA (Durucan and Brown 2000; Kang et al. 2011). Many studies have shown that PLGA polymer can favorably influence activity of cells essential for the formation and maintenance of bone tissue (Li et al. 2006; Bose et al. 2012).

Polymer component improves mechanical characteristics of composite and contributes to biological characteristics important for expression of specific cell properties during bone growth. On these principles hydroxyapatite composite scaffolds of calcium hydroxyapatite (CHA) and PLGA have been developed, so that PLGA is present as a thin layer on CHA scaffold. CHA is often used in bone tissue engineering because it has good mechanical properties, can be obtained as material of high purity, has good properties for processing and adjustable rate of degradation, all of which is important for adjustment to the healing rate of damaged bone (Agrawal and Ray 2001; Ngiam et al. 2009). The role of PLGA layer is multiple, because it can improve mechanical properties, and to be hydrophobic biological surface of scaffold essential for the various cell activities, such as adhesion, migration, release of metabolites, etc. (Thomas et al. 2014). Porous calcium hydroxyapatite scaffolds covered with PLGA has been showed significant biological advantages over standard bone substitute Geistlich Bio-oss® in in vivo studies of biofunctionality (Jokanović et al. 2016a). Thus, the composite biomaterials of calcium hydroxyapatite and PLGA can fulfill requirements necessary for good bone substitute with good mechanical properties, porosity, biodegradability, topological features, and with the ultimate goal to be osteoconductive and osteoinductive (Jokanović et al. 2016b).

New technologies in the development of potential biomaterial take into account the microenvironment necessary for cell differentiation because there are attempts at integration of active molecules, growth factors and drugs in the tissue matrix (Ripamonti 1993; Ignjatović et al. 2001; Najman et al. 2003, 2004; Vasiljevic et al. 2009, 2013; Mitić et al. 2014).

Examination of biocompatibility includes the evaluation of effects of physiologic environment on material and material on the environment. Evaluation of biocompatibility of biomaterials is possible through two aspects. The first aspect involves in vivo studies for assessing the overall biocompatibility of the newly synthesized biomaterials. In these cases primarily takes into account the physical and chemical characteristics of biomaterials its potential toxicity, biodegradability, the reaction between the tissue and biomaterials, toxicity genotoxicity and mutagenicity degradation products of biomaterials, etc. These tests primarily indicate possible directions of development in the synthesis of new materials that are used in medicine. Another aspect of biocompatibility includes testing the final product i.e. biomaterials to be used clinically to.

The core issue is such a new biomaterial behaves in the treatment of tissue deficits, and what is its biocompatibility and integrativity the tissue microenvironment and whether it supports the development of normal cells (Ohgushi et al. 1989; Ripamonti 1993; Najman et al. 2003, 2004; Vasiljevic et al. 2009, 2013). Today it is used for this purpose in vivo and in vitro experimental approaches which include a series of standardized experimental techniques (Council of Europe 1999; ISO 10993; National Institute of Health 1977).

2 Hypersensitivity Reactions to Biomaterials

In contact with organism, biomaterials represent foreign bodies and organism, in their presence, can react with them in various desirable and undesirable ways. Excessive and inappropriate immune responses to the presence of an antigen are called hypersensitivity or hypersensitivity reactions. Depending on the generated effectors molecules and mechanisms of their action to date have clearly defined four types of hypersensitivity reactions, while the fifth type is still subject of speculations (Rajan 2003).

Classification of hypersensitivity reactions according to Gell and Coombs (Gell and Coombs 1963):

Type I—IgE mediated hypersensitivity
Type II—cytotoxic—IgG/IgM mediated
Type III—immune complex mediated—IgG/IgM immune complex
Type IV—delayed hypersensitivity or cell mediated hypersensitivity.

Whether or not, in what way and to what extent the host will respond to the presence of biomaterials depends on the composition of the applied biomaterials, on

the site of application but largely depends on the physiological characteristics of the host organism. As response to biomaterials, only two types of hypersensitivity reactions are common, type I and type IV.

2.1 Type I of Hypersensitivity Reactions

This type of allergic reaction occurs immediately (within several minutes) after contact between allergens and IgE antibodies, which are already created in the body and which are present on the surface of mast cells and basophilic leukocytes. The reaction between antibodies and antigens results in the release of vasoactive amines, including histamine and adenosine, which causes the symptoms and signs of an allergic reaction of type I. The symptoms experienced by the patient can be very different depending on whether the allergen is injected, inhaled, or orally taken, and depending also on the dose of the allergen (Janeway et al. 2001). Immediate hypersensitivity reactions have diverse clinical and pathologic features, all of which are attributable to mediators produced by mast cells in different amounts and in different tissues. The manifestations of some common immediate hypersensitivity reactions are allergic rhinitis, sinusitis (increased mucus secretion; inflammation of upper airways, sinuses), food allergies (increased peristalsis due to contraction of intestinal muscles), bronchial asthma (bronchial hyperresponsiveness caused by smooth muscle contraction; inflammation and tissue injury caused by late phase reaction) and the most severe form anaphylaxis (fall in blood pressure caused by vascular dilation and airway obstruction due to laryngeal edema). Immediate hypersensitivity may be manifested in many other ways, as in development of skin lesions such as urticaria and eczema (Abbas and Lichtman 2010).

Reports of biomaterials evoking the IgE response are rare, although IgE reactions to some components of biomaterials encountered in other applications, such as nickel and chromium salts in occupational respiratory contact, are known and responses to silicone are controversial (Ratner et al. 1997).

Hypersensitivity type I diagnostic tests

If type I allergy is suspected, it can be diagnosed by a skin test prick (SPT). SPT involves intradermal inoculation of the allergen and provides evidence for sensitization to specific antigen. Results of this test can help in confirmation of the diagnosis of a suspected type I allergy. The main advantage of SPT as compared to an in vitro measurement of specific IgE antibodies is that the test can be interpreted within 15–20 min after the reagent is applied to the skin. Red, papular, and/or vesicular reactions of the skin may appear in positive test conditions. It is minimally invasive, inexpensive, results are immediately available and when carried out by trained health professionals, reproducible. The in vitro measurement of specific IgE antibodies (Pumhirun et al. 2000) is an important complementary tool to diagnose type I allergy, especially in subjects who cannot undergo SPT. For example, SPT is

not recommended in patients who have extensive eczema, dermographism, urticaria, or who are taking antihistamines or other medications which interfere with the proper interpretation of the test results. In vitro test methods may be less sensitive (Hill et al. 2004; Chung et al. 2010) and/or less specific (Ten et al. 1995; Van der Zee et al. 1988) than SPT depending on the method utilized and the allergens employed. Furthermore, in subjects with very high total serum IgE antibodies, low levels of specific IgE antibodies of doubtful clinical relevance are often detected. Moreover, SPT provides immediate information versus in vitro test results which may not be available for days or weeks. Thus, SPT has greater flexibility and is usually less costly (Heinzerling et al. 2013).

2.2 *Type IV of Hypersensitivity Reactions*

Type IV hypersensitivities are referred to as delayed type hypersensitivities because a reaction can typically take 12 or more hours to develop after contact with specific antigen (Brostoff et al. 1991). Reaction occurs after antigenic activation of a large number of TH cells (mainly TH1 subtype), in previously sensitized person, which then recruit other cells to the site of exposure. Sensitization develops only in some people after exposure to some certain antigens which can be inserted into the body in everyday life through food, water, skin, respiratory tract or different preventive, diagnostic and therapeutic procedures.

In evolution of type IV of hypersensitivity several phases were described: recognition and sensitization to antigen, TH lymphocyte activation and effector phase. The effector phase of a delayed-type hypersensitivity response is initiated by contact of sensitized T-cells with an antigen. In this phase, T-cells, which are antigen-activated, are characterized as TDTH cells and, in conjunction with activated antigen presenting cells (APCs), can secrete a variety of cytokines that recruit and activate macrophages, monocytes, neutrophils, and other inflammatory cells (Hallab et al. 2001). The main characteristics of type IV hypersensitivity reactions are localized inflammatory response which occurs after a period of latency after exposition to antigen to which person is sensitized. At the site of inflammation dominate presence of cells of which are the most numerous macrophages.

Type IV of hypersensitivity reaction is usually manifested in the skin in different clinical pattern.

In the last years, there were publications which can throw a new light on these complicated mechanisms leading to the development of the type IV of allergy, especially to drugs, nickel and other haptens and also can explain the differentiation of clinical pattern in respective patients. The skin symptoms in type IV of hypersensitivity are triggered by activation of specific T-cell CD4+ and CD8+. Immunohistochemical and functional analysis of reactive T-cell has shown that the delayed hypersensitivity reaction depends on the secreted cytokines. For the better understanding of these inflammatory cascades deleted type IV of hypersensitivity reactions have been re-classified into four main subtypes (Czarnobilska et al. 2007).

Clinically delayed hypersensitivity eruptions are often an overlap of cytokine pathways, with one preferential reaction dominating the final picture. Type IVa and IVc play a role in the mechanism of contact dermatitis, however type IV b in chronic asthma, chronic allergic rhinitis and maculo-papular exanthema with eosinophilia, type IV c in bullous reactions (i.e. Stevens-Johnsons Syndrome or toxic epidermal necrolysis), so type IV d in pustular exanthema reactions (i.g. AGEP—Acute Generalized Exanthematous Pustule, Behcet disease). This different clinical pattern of allergic disease mainly including drug allergy to nickel and other haptens as well as chronic asthma and allergic rhinitis may be explained by above mechanisms (Czarnobilska et al. 2007).

Hypersensitivity type IV diagnostic tests

For verification of type IV hypersensitivity reactions there are two common methods: (1) cutaneous patch testing and (2) lymphocyte transformation tests (Primeau and Adkinson 2001).

Cutaneous patch testing is considered as gold standard for in vivo evaluation of delayed hypersensitivity reactions (Schalock et al. 2012). It is commonly used for diagnostic purposes in people who already suspected hypersensitivity to the applied biomaterial, but also as preventive measures or determining predisposition to hypersensitivity reactions to different types of biomaterials. This procedure is not complicated, but it carries a certain discomfort for the patient. Also, although very small, there is a risk that the procedure itself, cause sensitization of the patient to the antigen used in the test. A patch test is always carried using some of the already defined batteries of antigens. Procedure of performing this assay consists of the introduction of the antigen in the vehicle such as petrolatum and the exposure of the skin (48–96 h) with the help of fixation bandage.

After exposition time, the reactions are graded on a scale from 1 (mild or absent response) to 4 (severe rash with small, possibly encrusted, weeping blisters) (Hallab et al. 2001). Practical advantages of cutaneous patch testing include ease of performance, rapidity of results, the scope of evaluation, and widespread availability (Granchi et al. 2006; Thyssen et al. 2011) These findings can be viewed as support for the argument that preoperative patch testing potentially prevents significant morbidity (Schalock et al. 2012). Its preoperative use should strongly be considered in patients with a history of metal allergies and its postoperative use in patients presenting with either suspected metal hypersensitivity or implant failure in the absence of infection (Schalock et al. 2012; Granchi et al. 2012).

Lymphocytes transformation testing (LTT) can be used as an alternative method to determine metal sensitivity in a patient. It has been suggested for use when patch testing provides questionable results. This in vitro test measures the proliferation of lymphocytes from a patient's peripheral blood in the presence and absence of a potential allergen (Schalock et al. 2012; Granchi et al. 2012).

An enhanced version of the lymphocyte transformation test, called memory lymphocyte immuno-stimulation assay (MELISA®), is available for healthcare practitioners and can assist in the detection of Type IV hypersensitivities, as

previously described (Valentine-Thon et al. 2006; Stejskal et al. 1996). In summary, a standard number of lymphocytes, with the exclusion of monocytes, are isolated from whole blood specimens for cell culture. The lymphocytes are cultured for 5 days then transferred to new plates containing known antigens, which are then pulsed for 4 h with methyl-^{3}H thymidine to quantify cell proliferation. A negative control is also obtained via lymphocytes from the same patient, which is not added to antigens. After culture, the lymphocytes are harvested onto filter paper and dried. The radioactivity present on the filter paper is measured in a liquid scintillation counter. A stimulation index (SI) is calculated by dividing the counts per minute (cpm) in the test well to the average cpm in the negative control wells (Valentine-Thon et al. 2007; Valentine-Thon and Schiwara 2003; Stejskal et al. 1996). A positive reaction, indicating Type IV hypersensitivity, is defined as a SI greater than 3 and an equivocal reaction is a SI between 2 and 3. A SI less than 2 is considered negative. Clinically, MELISA® has been proven to be an effective tool for the determination of sensitivities to various metals (Valentine-Thon and Schiwara 2003).

In vitro leukocyte migration inhibition testing involves the measurement of mixed-population leukocyte migration activity. Leukocytes in culture actively migrate in a random fashion, but they can be attracted preferentially to chemoattractants, such as those released by Staphylococcus and other bacteria. However, in the presence of a sensitizing antigen, they migrate more slowly, losing the ability to recognize chemoattractants, and are said to be migration-inhibited. Contemporary migration-testing techniques quantify the migration of lymphocyte populations in vitro through, under, or along media such as agarose layers, agarose droplets, capillary tube walls, membrane filters, and collagen gels (Hallab et al. 2000). Over the long term, migration testing alone (as well as any single assay) may be an inadequate detector of delayed type hypersensitivity (Repo et al. 1980).

2.3 Hypersensitivity to Orthopedic Materials

Orthopedic implants can be made of a variety of metallic, plastic, and/or ceramic elements. The metal components of knee prostheses are most commonly stainless steel, followed by cobalt-chromium molybdenum (CoCrMo) alloys, nickel, titanium, beryllium, vanadium, and tantalum (Basko-Plluska et al. 2011; Hallab and Jacobs 2009). Exposure to metal ions can occur in a number of ways. Routine metal exposure in humans occurs through skin contact with jewelry, cell phones, clothing fasteners, and leather and through occupational exposure, dental filings, and medical implants (Thyssen and Menné 2010). Individuals are further exposed to trace metals through smoking and in cosmetics, food, and drinking water (Ashraf 2012; Teow et al. 2011; Borchers et al. 2010).

Sensitization to metal is known to occur independently of the mechanism of exposure (Basko-Plluska et al. 2011). As previously mentioned, metal-ion exposure produces an adaptive immune response wherein macrophage activation leads to development of a delayed-type hypersensitivity reaction (Cadosch et al. 2009; Hallab et al. 2008; Thomas et al. 2000). Pathophysiological mechanism of hypersensitivity evolution to metals is not fully understood. It is believed that the metals in contact with body fluids corrode and set free metal ions which are processed by the immune system. These ions, although not sensitizers, form complexes with native proteins and act as allergens causing hypersensitivity reactions. Cutaneous reactions above the implanted device are primarily T cell-mediated type IV delayed-type reactions. Reported reactions at the site of the metal implant include type IV reactions but are probably complex in nature. Peri-implant reactions seem to be Th1-dominant (Schalock et al. 2012). Metals known as sensitizers (haptenic moieties in antigens) are beryllium, nickel, cobalt, and chromium; in addition, occasional responses to tantalum, titanium and vanadium have been reported (Hallab 2001). Nickel, cobalt, and chromium are the three most common metals that elicit both cutaneous and extracutaneous allergic reactions from chronic internal exposure, but almost all metals present in biomaterials can induce hypersensitivity reactions.

Hypersensitivity reactions to metallic joint implants can present in several ways and may result in localized or systemic allergic dermatitis, sometimes painful, and sometimes as exudative lesions in the periprosthetic region, loss of joint function, implant failure, and patient dissatisfaction (Thyssen and Menné 2010).

In patients with implants containing metal, the clinician should consider metal hypersensitivity when dermatologic allergic symptoms are reported. Furthermore, metal hypersensitivity should be considered in patients with joint implants when they have arthralgia, when periprosthetic radiolucent lines appear, or when aseptic implant loosening is observed (Willert et al. 2005).

In addition to the hypersensitivity of the metal components of the implants, in literature it is described hypersensitivity to the polymer components of the implants. The study of Gil-Albarova et al. (1992) demonstrated that lymphocyte-mediated immune response is activated in patients with aseptic loosening of cemented total hip prostheses. The most significant alterations were the high immune reactivity induced by the monomer of PMMA measured by the LTT, and the increase in total T lymphocytes (CD2 cluster), especially those displaying the interleukin-2 receptor (CD25) which is an early marker for lymphocyte activation. Although they did not perform immunological studies at the cement-bone interface membrane, the increase in total T lymphocytes, especially those displaying the interleukin-2 receptor, suggests the occurrence of a type IV immunological hypersensitivity reaction at that level (cell-mediated response or contact sensitivity). The high rate of lymphoblast transformation produced by PMMA indicates that only this substance, and not the bone cement stabilizers, acts as the allergen.

2.4 Hypersensitivity to Dental Materials

Materials that are routinely used in dentistry can give rise to hypersensitivity reactions in both sensitised patients and members of the dental team. The materials used in odontology includes antiseptics, metals, alloys, porcelains, impression materials, local anesthetics, cements, latex gloves, rubber dams, acrylates, adhesives, mouth washes, and others (Gawkrodger 2005; Khamaysi et al. 2006; Lygre 2002; Mallo-Pérez and Díaz-Donado 2003) Kanerva et al. (1995) identified more than 130 possible allergens derived from materials for use in odontology. In a study by Khamaysi et al. (2006) in patients with oral symptoms, who had undergone dental treatment, the common allergens detected included gold sodium thiosulfate (14.0%), nickel sulfate (13.2%), mercury (9.9%), palladium chloride (7.4%), cobalt chloride (5.0%), and 2-hydroxyethyl methacrylate (5.8%). In another study by Goon et al. (2006) the most common allergens in this group were the (meth) acrylate monomers and elemental mercury. Artificial and natural teeth, metallic dental implants, as well as restorative materials within the mouth interact continually with physiological fluids. They are subject to larger temperature and pH variations than most other parts of the body. Corrosion, the graded degradation of materials by electrochemical attack, is of concern particularly when dental implants are placed in the hostile electrolytic environment provided by the human mouth. Allergic reactions may occur from the presence of ions produced from the corrosion of implants. Typical allergic symptoms and diagnoses were Pustulosis palmaris et plantaris, lichen planus, stomatitis and contact dermatitis which implies that reactions to these materials appeared not only in the mucosa of the oral cavity, but also on the skin of entire body (Gawkrodger 2005; Hamano et al. 1998; Yanagi et al. 2005).

2.5 Endovascular Devices

As endovascular devices coronary stents, perforated foramen occluders, pacemakers and implantable cardioverter defibrillators are frequently used. Hypersensitivity reactions to the biomaterials used in endovascular prostheses are among the infrequent and unpredictable reactions that may lead to local or systemic complications following cardiovascular therapeutic interventions (Honari et al. 2008). A spectrum of responses, varying from benign reactions to excessive inflammation and systemic hypersensitivity reactions are reported and should be considered relative to the context of their application (Nebeker et al. 2006; Fukahara et al. 2003; Dasika et al. 2003).

3 Effects of Biomaterials to Implantation

Implantation to assess the impact biomaterial on the structure and function of tissues. Evaluation of the effect of the implant includes primarily microscopic evaluating. Microscopic evaluation includes monitoring a large number of biological parameters e.g. thickness and vascularization of fibrous capsule, the number and size of inflammatory cells, cell infiltration in implant, degenerative and necrotic changes in the surrounding tissues, apoptosis, cell proliferation and differentiation, endothelialization, biodegradation, the formation of thrombus, calcification (Ignjatović et al. 2001; Najman et al. 2003, 2004; Vasiljevic et al. 2009, 2013; Ignjatović et al. 2013). As experimental models used for implantation mice, rats, rabbits, guinea pigs, dogs, sheep, goats, pigs or other animals. The implantation site are the subcutaneous tissue, muscle, bone or intraperitoneal. Evaluation of results is done in the short term at 2, 4, 6, 8, 12 weeks or long term several months.

Local effects of biomaterials at the site of implantation

After implantation, which represents a kind of tissue injury, biomaterials initiate a host response which begins with blood-biomaterial interactions and provisional matrix formation and continues with acute/chronic inflammation, granulation tissue emergence, foreign body reaction, development of fibrous capsule and possible fibrosis (Anderson et al. 2008). All aforementioned events are interrelated and are partially overlapped. The course of these processes depends on the characteristics of implanted biomaterial, but likewise final fate of this same biomaterial depends on intensity of particularized host tissue reactions.

3.1 Injury

Implantation of biomaterial represents an injury per se because it leads to tissue damage. At the very beginning of host response to tissue injury, predominantly blood and vasculature are involved (Anderson 2008). Cells, growth factors, cytokines and chemokines from blood affect initiation of inflammatory response whose direction and intensity are extremely important for proper healing of injuries (Shapiro 2008). Bleeding and coagulation at the site of implantation are starting events of healing cascade that further follows the order Inflammation-Repair-Remodeling. How will host tissue respond to injury depends on its degree and is in correlation with blood-biomaterial interactions, formation of provisional matrix and inflammatory response. Further, extent of granulation tissue formation, foreign body reaction and fibrosis/fibrous capsule development in implants depends on the aforementioned factors. All of these processes are, in the case of biocompatible biomaterials, ending within 2–3 weeks after implantation (Anderson 1988, 1993).

3.2 Blood-Biomaterial Interactions

After implantation, biomaterial comes in contact with blood which coagulates (Yu et al. 2014; Shiu et al. 2014). Blood plasma, among others, is consisted of approximately three hundred distinct proteins, whereby many of them are involved directly in wound healing process (Powanda and Moyer 1981; Anderson and Anderson 2002). Immediately after implantation, adsorption of proteins from blood and interstitial fluids to the biomaterial surface occurs (Franz et al. 2011). This is also confirmed by the results of our investigations which are showing that after one-week incubation of biomaterial in simulated body fluid (Kokubo 1996) weakly soluble precipitates can be noticed on surface of biomaterial (Vukelić et al. 2011, 2012). Since layer of adsorbed proteins has influence on coagulation, complement system, platelets and finally immune cells, blood-biomaterial surface interactions have a great impact on host inflammatory response to implanted biomaterial (Anderson 2008; Franz et al. 2011; Yu et al. 2014). Blood is a rich source of different cytokines and growth factors, whereby many of them have proangiogenic properties. This fact is very important from aspect of injury healing, because vascularization and angiogenesis are key events that maintain tissue structure and repair process (Najdanović et al. 2015). It is probably that proangiogenic factors from blood affect various cell types involved in vascularization and angiogenesis. So, implants made of nanomaterial NP-CP/DLPLG mixed with full blood and bone marrow cells are better vascularized in regard to implants made of nanomaterial and blood only, 8 weeks after subcutaneous implantation (Janićijević et al. 2008). Blood plasma in combination with biomaterial can be very useful in the field of tissue regeneration as well, according to our previously findings (Ajduković et al. 2005). Our recent results from experiments with subcutaneously implanted biomaterial mixed with blood plasma and adipose-derived stem cells indicated that this concept can be suitable for increasing vascularization (Najdanović et al. 2015).

Textured biomaterial surfaces, in contrast to smooth surfaces, promote coagulation by interrupting the blood flow at the blood-biomaterial interface. It is also known that protein adsorption occurs more on hydrophobic than hydrophilic surfaces (Wilson et al. 2005). Chemical composition of absorbed proteins does not remain constant and successively replacement of adsorbed proteins which happened during time is termed the Vroman effect. It occurs mostly on negatively charged hydrophilic surfaces (Turbill et al. 1996). Deposition of blood proteins on a biomaterial surfaces represent an introduction into provisional matrix formation (Anderson 2008).

3.3 Provisional Matrix Formation

Provisional matrix, constituted mainly of fibrin and fibronectin, arises as a consequence of vascularized tissue injury during biomaterial implantation. It serves as

matrix for cell adhesion but also stimulates them to proliferate, differentiate and synthesize new extracellular matrix components (Anderson and Patel 2013). Fibrin forms the basis of provisional matrix, but beside fibrin, secretory products of complement system, activated platelets, inflammatory and endothelial cells also contribute to provisional matrix structure. Over and above, biomaterial surfaces spontaneously adsorb fibrinogen, precursor of fibrin (Hu et al. 2001). As a component of provisional matrix, fibrin network initiate recruitment of inflammatory cells and fibroblasts. Beside fibrinogen/fibrin, fibronectin and vitronectin have also been described to attach to biomaterial surfaces (Asch and Podack 1990; Gawaz et al. 1997; Lee et al. 2006). Phagocytes are attracted by adsorbed fibrinogen/fibrin, initiating an inflammatory response which occurs physiologically after clot formation (Jennewein et al. 2011). Further, fibronectin and vitronectin regulate inflammatory response to biomaterials by promoting macrophage fusion to foreign body giant cells on biomaterial surfaces. Activated platelets from formed blood clot attract fibroblast through platelet factor 4 (PF4), platelet-derived growth factor (PDGF) and transforming growth factor-beta (TGF-β) release (Riches 1988; Wahl et al. 1989). Thrombin from blood clot, also acts as a chemoattractant for neutrophils, monocytes and lymphocytes by affecting regeneration of damaged tissue (Bar-Shavit et al. 1983; Bizios et al. 1986). So generally, the provisional matrix is composed of adhesive proteins as well as released platelet granule components which besides the above mentioned factors include also thrombospondin, transforming growth factor-alpha (TGF-α) and platelet derived endothelial cell growth factor (PD-ECGF). In this way, fibrin network provides favorable substrate for cell adhesion and migration. Depending on the biomaterial environment at the site of implantation, adherent proteins may promote chronic inflammation or wound healing process (Anderson 2008; Franz et al. 2011).

Attracted phagocytes degrade fibrin network over time, which at the beginning promotes inflammation (Szaba and Smiley 2002) and later fibrin network is gradually being replaced by immature connective tissue which contains immature fibroblasts (cells that are often referred to as mesenchymal stem cells) with the ability to differentiate into various cell types (Alberts et al. 2002). Existence of immature connective tissue in the implant site is of the great importance to the process of reparation and regeneration in general.

3.4 Inflammation

Inflammatory process involves a series of interrelated events that participate in tissue healing and tissue reconstitution at the site of implantation. Its intensity and time duration depend very much on the size, shape and physicochemical characteristics of biomaterial. Inflammatory process is also influenced by extent of injury during implantation procedure and type of injured tissue. At the beginning of host inflammatory reaction, neutrophils followed by monocytes and macrophages are the

most prevalent cell types (Anderson 2001). Inflammatory response triggered by implanted biomaterials can be acute and chronic.

Typical feature of acute inflammatory response, which lasts from minutes to days, is migration of neutrophils and eosinophils to the site of implantation, mast cell degranulation with histamine release and adsorption of fibrinogen to biomaterial surface (Tang et al. 1998; Zdolsek et al. 2007). The major role of neutrophils and subsequently macrophages is to phagocyte microorganisms and foreign materials, and the extent of degradation depends on the properties of biomaterial itself (Anderson 2001). For instance, extended resorption by phagocytes can be a consequence of biomaterials hardness (Najman et al. 2004). Histamine released from mast cells is critical to the recruitment of phagocytes to implanted biomaterials (Tang et al. 1998). Adsorbed and partially denatured proteins, predominantly fibrin/fibrinogen are considered to be ones which determine stream of the acute inflammatory response (Tang and Eaton 1993; Anderson 2001). These proteins induce and modulate leukocyte migration and inflammatory reaction (Jennewein et al. 2011).

Chronic inflammation also begins with recruitment of neutrophils, but in contrast to acute inflammation it is histologically heterogeneous and may cause implant failure. It is predominantly characterized by the presence of macrophages, monocytes, lymphocytes and fibroblasts which become numerous 1–2 weeks after injury and diminish at 6 weeks. Proliferation of blood vessels and development of connective tissue are also characteristics of acute inflammatory response. Surgical wounding per se is enough to attract neutrophils, and presence of biomaterial increases macrophage migration to the site of implantation (Robitaille et al. 2005). Macrophage represents the most important cell type in chronic inflammation. These cells produce the great number of biologically active factors which can affect all aspects of tissue reparation and regeneration after injury (Anderson 2001). It is believed that macrophages and their products are key factors in controlling wound healing and fibrosis (Anderson and McNally 2011). Prolonged chronic inflammation is often cause of impaired wound healing around implanted biomaterial (Dee et al. 2003), and intense inflammatory response usually leads to implant failure. However, the inflammatory response is the first in a series of reactions that lead to normal tissue healing, and in the last few years there has been increasing evidence that controlled inflammation may have beneficial effect on reparative and regenerative processes. Results from our study, among others, showed that inclusion of thioglycollate-elicited peritoneal macrophages in structure of implants composed of mineral bone substitute may support osteogenic process (Živković et al. 2015).

3.5 Granulation Tissue

With regards to biomaterials with good biocompatibility, inflammatory response usually lasts no longer than 2 weeks. Resolution of acute and chronic inflammatory responses is followed by granulation tissue formation that results from proliferation

of fibroblasts and vascular endothelial cells, and is identified by the presence of macrophages, infiltrated fibroblasts and blood vessels. This tissue was named "granulation" according to its granulated look and presence of numerous capillaries (Nowak and Olejek 2004). Formation of granulation tissue after inflammatory response represent hallmark of tissue healing.

Thanks to numerous blood vessels, different cells, cytokines, chemokines and growth factors are coming to the site of biomaterial implantation. Fibroblasts from granulation tissue proliferate and synthesize collagen, elastin, proteoglycans, glycosaminoglycans and other noncollagenous proteins (Lin et al. 1997; Olczyk et al. 2014). Granulation tissue is being subsequently remodeled approximately 7–10 days after injury. This process results in the formation of mature connective tissue (Häkkinen et al. 2012).

One should make a distinction between the terms granulation tissue and granuloma, accumulations of modified macrophages called epithelioid cells. Granuloma is a consequence of chronic inflammation, while granulation tissue is a normal occurrence during tissue healing. A few cell layers usually separate granulation tissue from the implanted biomaterial (Anderson and Patel 2013). Fibroblasts that granulation tissue contains allow contraction and wound closure.

As noted, granulation tissue formation goes along with normal tissue healing process. However, in the case of large tissue injury, abundant granulation tissue forms in an attempt to fill defect, leading frequently to fibrosis or scar formation (Lin et al. 1997; Anderson 2001).

3.6 The Foreign Body Reaction

Macrophages that have attached to foreign biomaterial over time, have a strong ability of phagocytosis and secrete proinflammatory cytokines, Reactive Oxygen Species (ROS) and degradative enzymes. These cells can resorb particles up to a size of 5 μm. In the case of larger particle size, macrophages fuse into foreign body giant cells (Franz et al. 2011). Foreign body reaction involves macrophages, foreign body giant cells and components of previously formed granulation tissue. The normal foreign body reaction can be seen often when biomaterials are implanted, but prolonged reaction can inhibit healing process (Anderson 1988).

There are two morphologically different types of foreign body giant cells, refer as the Langhans type and the foreign body type. The first cell type formation is stimulated by Interferon- γ (IFN-γ). These cells are characterized by round shape appearance and presence up to approximately 20 nuclei. Nuclei are located in peripheral cell region and are arranged in a circular form. The second cell type formation is stimulated by Interleukin-4 (IL-4) or IL-13. These cells have an irregular shape and randomly arranged numerous nuclei (more than 20) (Fais et al. 1994; DeFife et al. 1997; Anderson 2000; Kaji et al. 2000).

During the foreign body reaction, reorganization of previously formed extracellular matrix occurs. Family of enzymes called matrix metalloproteinases

(MMPs) participate in this process, degrading almost every extracellular matrix component (Luttikhuizen et al. 2006). MMPs are secreted by macrophages, while new extracellular matrix components are secreted by fibroblasts. Extracellular matrix represents a rich milieu of different cytokines, chemokines and growth factors which are released by remodeling process. Further fate of cells and processes in the tissue at the site of biomaterial implantation depends very much on the features of these released factors.

Foreign body reaction is greatly determined by the form and surface topography of implanted biomaterial. Porous materials, particulate or microspheres are characterized by significant foreign body giant cell reaction, in contrast to the smooth-surface biomaterials (Anderson 2013).

3.7 Fibrous Capsule Development and Fibrosis

Degradable biomaterials will be resorbed through chronic foreign body reaction. The final outcome of foreign body reaction in the case of non-degradable materials is formation of fibrous capsule around the implant (Luttikhuizen et al. 2006).

Ideal result of implantation would be complete restoration of normal tissue architecture and function after healing of injuries. However, formation of fibrous capsule (usually 50–200 μm in thickness) is generally the final step in the reaction of host tissue to biomaterial (Morais et al. 2010; Anderson and McNally 2011). The reason for this is that organism recognizes the implanted biomaterial as foreign body that should be isolated. This is best accomplished by forming a thin capsule that can be tolerated around the implants, because it prevents prolonged interaction between implanted biomaterial and the host tissue (Konttinen et al. 2005; Nuss and Rechenberg 2008). Fibrous capsule is built primarily of collagen III, produced by fibroblasts that originate from granulation tissue. Presence of thick connective capsule around implants may indicate a strong inflammatory response (El-Warrak et al. 2004a, b). Fibrous encapsulation and fibrosis may result in rejection of the implanted biomaterial (Anderson 2008).

Although inflammatory phase caused by biomaterial implantation is usually followed with fibrosis, these two events are not necessarily mutually proportional (Jones 2008). It could be said that the extent of fibrosis depends primarily on types of different factors found at the site of implantation, which influence inflammatory response. Among the most significant factors that influence the extent of inflammation and fibrosis are IL-1, TNF-α and TGF-β. Overexpression of IL-1β can be the cause of strong inflammatory response that can evolve into a prolonged inflammation which leads to tissue damage and fibrosis. TNF-α overexpression leads to inflammation whose consequence is weak fibrosis. Unlike these, overexpression of TGF-β is cause of mild inflammatory response but strong and progressive chronic fibrosis (Jones 2008).

Macrophages are able to secrete all mentioned cytokines, as well as many other factors and therefore are often referred as key regulators of fibrosis. Thanks to these

secretory factors macrophages recruit fibroblasts, other inflammatory cell types as well as additional macrophages to the site of tissue damage due to the implantation procedure. Ingestion of apoptotic and dead cells in general increases macrophage TGF-β secretion, in this case directing them towards profibrotic manner. On the other hand, macrophages can also promote resolution of fibrosis through clearing of fibroblasts, other type of cells and cellular debris, thereby eliminating profibrotic stimuli (Wynn and Barron 2010).

For many years fibrosis was thought to be a progressive and irreversible process, but it is not necessarily the case. In this regard, ongoing inflammation can reverse fibrosis by virtue of macrophages collagenases that enable degradation of extracellular matrix. Bearing in mind both profibrotic and antifibrotic activity of macrophages, management of the functional state of these cells could be a tool to control fibrosis (Wynn and Barron 2010).

4 Conclusion

Implantation of biomaterial is followed by series of dynamic and interrelated processes as a consequence of local reaction of organism, considering that surrounding tissue is injured and comes into contact with a foreign body. Effects of biomaterial at the site of implantation depend on its size, shape, surface and physicochemical characteristics. Macrophages are cells that regulate the host response to implanted biomaterial at several levels. It is therefore logical that, in future, researching should be focused on these cells in order to improve biomaterials' acceptance which could be useful in tissue engineering and regenerative medicine.

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