БИОХИМИЧЕСКИЕ АСПЕКТЫ ТВЕРДОФАЗНЫХ СОЕДИНЕНИЙ

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Innovative functionally-active synthetic implant coatings are needed to program immune reactions

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The common and life-threatening like cancer and cardiovascular disorders, as well as consequences of severe trauma require treatment based on implants, transplants and implantable biomedical devices. The perspective way is to optimise therapeutic implantation program for each individual patient in advance, using minimal non-invasive and low-cost approaches. A complex view about achieving an interdisciplinary approach and required bringing together most advanced expertise and technology of biomedicine, chemistry, physical and mathematic is presented in a paper.

Keywords: *implant coatings; immune reaction; like cancer and cardiovascular disorders.*

Number of human pathologies, including most common and life-threatening like cancer and cardiovascular disorders, as well as consequences of severe trauma require treatment based on implants, transplants and implantable biomedical devices.

Thus, for example, mechanical circulatory support device, most often used to assist the left ventricle (LVAD, left ventricular assist device), is a key therapeutic solution for the patients with advanced heart failure – affecting 2–3% of the adult population and 6–10% of people above 65 years old. Heart failure (HF) is a major health economic factor, it is the reason for 5% of all hospitalizations in Europe and other developed courtiers world-wide. The prognosis of HF is discouraging with less than 50% of patients surviving 5 year after the first symptoms of the disease are identified. The terminal state of advanced HF is characterised by shortness of breath, lung edema, dizziness, tiredness (fatigue) and weakness, weight gain due to swelling, rapid or irregular heartbeat and chest pain.

Before recent advance in implantation, the only promising solution for the patient suffering from terminal state of advance HF was organ transplantation. However, due to obvious reason – limited access to organ that can be used for transplantation – for most of patients the chance to obtain new heart in time was extremely low. Initially, LVAD was designed as a bridge for transplantation that significantly –

for several years – increased the ability of the patient to wait for the new heart [1]. Further successes in the construction of implantable LVAD allowed to use it not only as bridge for transplantation, but also as therapeutic solution resulting in heart recovery in up to 50% of patients, that can be removed after couple of years allowing the patient to live with own hart.

Implants are most frequently constructed from non-degradable metallic and polymeric materials. Despite our recent progress in the construction of implants, number of patient still suffer from implant intolerance, failure, chronic inflammation, pain and recurrent infections. One of major problem in implantation is foreign body response caused by local and tissue-specific macrophages. Macrophages are designed by nature and trained by long-term evolution to recognise all foreign bodies and to make all the efforts in order to eliminate them [2]. First, macrophages try to engulf foreign particles and degrade them by special intracellular organelles: phagolysosomes [3]. However, the size of implant, that is much larger than the size of a single cell-macrophages does not allow to complete this process, macrophages continuously repeat these attempt and finally stay in a so-called activation state of “frustrated phagocytosis”, characterised by the release of tissue-destroying and pro-inflammatory molecules [4].

In case of LVAD, despite recent progress in the surgical procedure and implant construction, implantation is still associated with significant morbidity and mortality during follow-up, with inflammation-induced thromboembolic events being one of the main causes [5]. There is an urgent need to develop innovative solutions in the constructions of implantable LVAD, made out of the best tolerated by our body metal-titanium to suppress inflammation around the cannula and to reduce the risk for thromboembolic events.

Not only titanium implants, but all implanted materials are able to induce a foreign body response (FBR) which is primarily mediated by macrophages. The severity of reaction on the nature of the implanted material, its structure, surface topography and localization in the specific tissue organ is very important. Moreover, for each type of implant each patient ill develop individual reactions, which will depend not only on the genetic predisposition, but also on the age, presence of chronic inflammatory disorders, in distant organs, diet, life style and even the level or stress.

Several biomaterials based on non-biofouling surfaces, natural polymers for improved interaction with the host tissue or surfaces actively releasing anti-inflammatory drugs / bioactive agents have been developed to reduce implant-induced inflammation [6]. However, no definitive and long-term solution to avoid adverse immune responses to the implanted materials is available to date.

Preventing of implant-associated infections or chronic inflammation via manipulating macrophage phenotype is the most promising strategy to improve implant acceptance by the patient. This control over macrophage activation can be achieved by innovative technological solution: construction of functional, biologically active implant coatings. Such coatings have to be designed to control immune reactions not only on the initial acute inflammation caused by trauma induced implantation but also on the long-term basis. Up to date, analysing compatibility and usefulness of implant coating materials 3 major parameter have been evaluated: mechanical properties, toxicity for somatic cells and; in some cases, direct anti-bacterial properties. And, despite number of indications about detrimental reactions of innate immune system to the implants, examination of the effect of coating material on the macrophages reactions and programming was neglected.

First necessary step in this direction is prediction of personalised responses to coated implant surface by ex vivo identification of adverse immune reactions, prediction of potential inflammatory complications and selection of the best coating type for each individual patient. Pioneering study for the design of ex vivo test-system based on human primary monocytes-derived macrophages has been performed by collaborative team from Tomsk State University, Tomsk Polytechnic University and University of Heidelberg, Germany [7]. We were able to identify critical parameters indicating profile of individual inflammatory response to the surface modification of biomaterials based on high-molecular polylactic acid, and to predict which out of brilliant green dye-modified materials, that showed improved thermal stability and good mechanical properties, will interact with innate immune system of specific individuals with minimal inflammatory consequences. However we were surprised to find out that all these modifications can induce some inflammatory reactions in macrophages.

Therefore, the most challenging task in future is design and synthesis of functional implant coatings that have to provide stability, tissue-specific compatibility, long-term control over local immune reactions and, ideally, also support tissue-specific regenerative processes.

Such a complex goal can be achieved only as an interdisciplinary approach and required bringing together most advanced expertise and technology of biomedicine, chemistry, physical and mathematic. Our ultimate aim is to be able to develop mathematic approach for the simulations of individual responses to implant coating and the application of such simulation programs to optimise therapeutic implantation program for each individual patient in advance, using minimal non-invasive and low-cost approaches.

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