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Bio-inspired assembling/mineralization process as a flexible approach to develop new smart scaffolds for the regeneration of complex anatomical regions

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ABSTRACT

Bio-inspired synthesis of smart biomaterials is an emerging nano-technological approach to develop new solutions for an ever-raising number of patients affected by degenerative and disabling pathologies. Particularly for purpose of tissue regeneration, the new materials should function as scaffolds with high mimicry of host tissues, in order to instruct cells to perform their task. Due to the complexity of living tissues and limitations of the current fabrication methods, synthesis methods reproducing the biologic processes may exploit the huge information inherent in macromolecular matrices, to build complex nano-composites with regenerative ability. As an example the assembling/mineralization phenomena involved in hard tissues can be mimicked to achieve smart devices able to regenerate different tissues such as joints and periodontium. Besides, the implementation of this approach with remote activation by low magnetic fields of bio-resorbable superparamagnetic apatite nano-phases, may provide new devices enabling activation *on demand* suitable for non-invasive and more effective therapies.

1. Introduction

The steady increase of the number of clinical cases related to disabling pathologies or traumas affecting the musculoskeletal system, and the consequent growth of socio-economic costs are pushing toward the development of new therapeutic approaches addressed to a complete tissue regeneration. In fact, the most serious and disabling diseases affecting hard tissues such as bone, cartilage and teeth, cannot be adequately solved by most of the conventional approaches that often results in temporary benefit and only partial recovery of the initial functionality, as well as in possible side-effects making necessary additional surgery and subsidiary interventions that further raise the sanitary costs. Moreover, the progressive ageing of the population, the increase of the life expectancy and the need to maintain an active lifestyle will further raise the sanitary costs in the next decades.

One of the most serious degenerative diseases affecting the musculoskeletal system, is the osteoarthritis (OA) that mainly affects osteo-cartilaginous tissues of the joints, which are composed of a subchondral bony part, surmounted by a mineralized cartilage that evolves into hyaline cartilage, a non—mineralized tissue responsible of the wear resistance of the joints [1]. These components act synergistically to provide complex biomechanical performance and, very often, damaging involves the whole anatomical compartment. OA results in progressive deterioration and sclerosis of articular cartilage and subchondral bone and changes in the synovial membrane as a result of mechanical and biological processes that modify cartilage homeostasis [1–3]. OA has a major impact on patient mobility, productivity and independence and ranks among the top ten causes of disability worldwide [4]. With the population aging, the prevalence of OA is increasing and its consequences are impacting significantly on society. Numbers are impressive, accounting for over 20 million diseased people in the USA and over 50 million in Europe, expected to double by the year 2020. Moreover, one third of the European population will be at least 60 years old by 2050 and the increased physical activity and modified lifestyle provoke a high incidence of these diseases even in the young population. Costs of OA-related illnesses have risen over recent decades accounting for up to 1–2.5% of the gross national product in developed countries. OA is the leading indication for joint replacement surgery; 905,000 knee and hip replacements were performed in 2009 at a cost of $ 42.3 billion [5]. Currently

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available pharmacological solutions, including topical agents used in patients as adjuncts or as systemic medications, suffer from limitations and they can only lead to the short-term reduction of mild-to-moderate pain in non-severe chondropathies [6]. In addition, anti-inflammatory drugs present potential side-effects and require close patient monitoring due to toxicity (including renal disease, hepatotoxicity, cardiovascular and gastrointestinal toxicity). Injectable visco-supplements that mimic healthy synovial fluid are also of limited efficiency and can provoke side-effects when abused or misused [6]. As the current pharmacological therapies, as well as the recourse to prosthetics, are not satisfying for the definitive and complete functional recovery of the diseased part, new regenerative approaches shall be addressed to the healing of osteo-cartilaginous tissue complexes (Fig. 1).

Similarly to the joints, the periodontium is a complex anatomical region of dental tissue composed of mineralized tissues such as alveolar bone and cementum, and the non-mineralized periodontal ligament (PDL), which are responsible of the stability and resilience of tooth in its alveolus (Fig. 2) [7]. Periodontium can be affected by degenerative diseases such as periodontitis, a major chronic disease with a prevalence similar to cardiovascular disease and diabetes. Periodontitis provokes the loss of healthy teeth and limits the possibility to use dental implants. Besides, periodontitis can generate secondary serious problems affecting cardio-circulatory and breathing system, as well as diabetes [8–16]. According to the Oral Health European Platform, around 50% of the European population suffers of periodontal diseases and according to recent findings from the Centers for Disease Control and Prevention (CDC), 47.2% of American adults have mild, moderate or severe periodontitis that raises up to 70.1%, in aged people [8].

In cases of severe periodontitis spontaneous tissue regeneration does not usually occur on a clinically predictable basis, and the existing therapies are still not adequate for complete regeneration of the periodontium with all its functions. For this reason, adequate approaches for periodontal regeneration should be grounded in a biologically directed process, thus involving all cellular components of the periodontium: fibroblasts for soft connective tissues such as PDL, cementoblasts for cementogenesis, osteoblasts for bone, and endothelial cells for angiogenesis [17]. Besides periodontium, dentine and enamel are very often damaged by demineralization and degeneration following exposure to bacterial toxins during carious progression that, in the long term, may provoke the tooth loss [18]. Dental caries has historically been considered the most important component of the global oral disease burden as in most high-income countries the disease affects 60–90% of school-aged children and nearly 100% of the adult population in the majority of countries [19,20]. So far, dentin and enamel reconstruction is based on the mere apposition of resins on the residual dental issue [21]. Therefore, similarly to what desired for regeneration of multifunctional tissues of joints, new regenerative approaches addressed to the whole dental complex shall be developed [17,22–25].

When hard tissue regeneration cannot occur spontaneously, due to large size defects, surgeons are required to use bioactive scaffolds bridging the gap between the bone stumps and enabling an active cross-talk with cells, thus inducing adhesion, proliferation and specific regenerative differentiation [26]. To this purpose, scaffolds have to closely mimic chemical composition and 3D porous morphology of the native tissues to finally exhibit adequate activity with respect to cells in relevant environment, thus resulting in a progressive resorption of the scaffold while reconstructing new healthy tissue. So far, in spite of the recent development in material science to develop new materials and processes, many challenges are still open to obtain bioactive constructs with complex 3D structure. In this respect a key limitation is given by the high complexity of the chemistry and morphology of native human tissues, which enables the exchange of biochemical and topological information with cells that drives the formation and maturation of new tissue. Most of the current approaches for biomaterials development make use of crystalline ceramic materials, synthetic polymers (particularly the ones capable of resorption in vivo but not really mimicking the native tissues), as well as of forming processes, that even when based on guided manufacturing (e.g., 3D printing), suffer of limited spatial resolution and cannot deal with the huge amount of information inherent in the composition and structure of bone, cartilage and dental tissues.

2. Biomineralization as a smart nanotechnology from nature

Since a decade material scientists are investigating natural materials and processes with ever increasing interest to draw inspiration for the development of new synthesis methods to achieve enhanced control in design and synthesis of new smart devices [27–29]. Particular attention is addressed to biomineralization which is a complex cascade of phenomena used by natural organisms to generate hybrid nano-structured materials (i.e., inorganic nanocrystals grown on organic templates), with hierarchical organization from the molecular to the macroscopic scale, that function as endoskeleton (in mammals), exoskeleton (in insects and crustaceans) and protective shell (in molluscs), and masticatory systems (i.e., the teeth in vertebrates) [30].

The development of these complex structures represents an example of nanotechnology from nature, that pins on the exchange of chemical-physical and topological information at the molecular level between the organic macromolecule, acting as a template, and

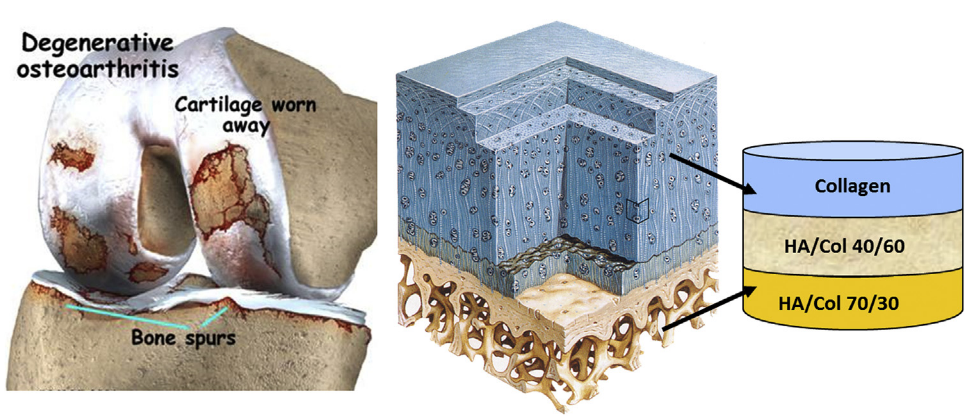

Fig. 1. Scheme of osteochondral defect involving the whole osteocartilaginous region of joint.