Chapter 2
Remarkable Body Architecture of Marine Sponges as Biomimetic Structure for Application in Tissue Engineering

Eva Martins, Miguel S. Rocha, Tiago H. Silva and Rui L. Reis

Abstract Recent advances in the study of marine environment, particularly of marine organisms' architecture and composition, have isolated interesting compounds as proteins, GAG-like polysaccharides and bioactive compounds. These compounds have allowed the development of panoply of biomaterials inspired by morphological characteristics and anatomical structures of the marine species. Besides, the scientific community acknowledges the enormous biotechnological potential in the marine resources that can be a promising effective and efficient alternative to be used in Human health, namely tissue engineering and regenerative medicine, as well as to support the progress in pharmacological, cosmetic, nutraceutical and biomedical fields. Additionally, sustainable ways are being applied to explore these marine resources and address biomimetic approaches, aiming to take the most out of the astonishing marine environment in ecologically compatible ways. Marine sponges are a particular group of organisms feeding these biotechnological developments for human health, both as source of new drugs or inspiration for the development of marine biomaterials. This chapter aims to demonstrate, in a concise and clear way,

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the biotechnological potential of marine sponges used as susceptive bioscaffolds for regenerative medicine and biomedical applications in general.

Keywords Marine sponges · Skeletons · Skeletal elements · Spicules · Collagen · Chitin · Biosilica · Polyphosphates · Biomineralization · Tissue engineering · Biomimetic materials · Biomedical application · Bone · Marine biomaterials · Marine biotechnology

2.1 Introduction

The marine environment provides an abundance of resources and its valuable biodiversity is a potential source of new beneficial products for society, including products for biotechnological and biomedical applications. Surprisingly, marine organisms remain a largely unexplored resource, although a growing interest in this promising field is changing this scenario. Among the marine organisms, marine sponges present a particularly interesting therapeutic potential. These sessile animals classified into the phylum Porifera dating from over 580 million years, developed an important evolution feature by established symbiotic interactions with surrounding microorganisms to protect themselves from pathogenic agents, possessing a broad range of molecules with different effects such as antitumor, antiviral, anti-inflammatory and antibiotic effects [1, 2]. In fact, one-third of the compounds obtained from marine organisms in the last 50 years is obtained from this phylum [2].

In addition to the impressive chemical properties, sponges present outstanding structural features, an inspiration for the emerging area of tissue engineering, an interdisciplinary field mainly focused in the regeneration of functional human tissues by engineering tissue templates mimicking the architecture and functional properties of extracellular matrix (ECM), known as scaffolds, that will support cell growth and differentiation towards net tissue formation. Thus, the development of innovative tissue engineering technologies can benefit greatly from the study of high-performance biostructures and the smart design of marine sponges [3]. Tissue engineering has been studied as a step further to current therapies, corresponding in fact to a change of paradigm, from substitutive medicine to regenerative medicine. Nowadays, the medical procedures for repairing critical injuries that the body could not regenerate by itself are the replacement of the damaged tissue with synthetic prostheses and tissue grafts. However, these clinical practices have numerous complications associated, as potential harmful immunological responses, high medical treatment costs and a limited number of the donor tissues, which prompted the development of tissue engineering procedures [4].

The abovementioned scaffolds have important biological features in tissue engineering strategy, as they maintain a matrix for tissue regeneration in vivo while providing a 3D physical support for cell culture in vitro, thus mimicking more closely the in vivo conditions of the tissue to be replaced than cellular monolayers [5]. However, these scaffolds require specific features, such as adequate biodegradability, low immunogenicity and cytotoxicity, suitable pore size (100–600 μm) and pore interconnectivity (porosity > 50 Vol.%) to support cell growth, differentiation and migration [6].

The combination of these demanding properties is hard to achieve and the selection from a vastness of raw materials, ranging from ceramics and polymers to composites, is difficult and present limitations to their use in the preparation of perfect biomaterials. These limitations are being tackled by using natural materials, which provide an interactive surface for cell attachment, growth, and differentiation, while being more biocompatible and biodegradable than synthetic-made materials, as natural-based materials are more similar to the tissue components being mimicked.

Marine sponge skeletons possess noteworthy materials in their composition suitable for tissue engineering such as biosilica, polyphosphate, collagen/spongin and chitin [7, 8]. These are being considered particularly for bone tissue engineering strategies, since the first two inorganic polymers can induce osteogenesis in vitro thus favoring mineralization [9], while the latter two are promising biomaterials for the development of new scaffolds, being a similar and safer alternative than mammalian collagen [10, 11].

Just as previously stated, the developed scaffolds require a suitable structure in order to support cell growth and migration along the whole material network. In this context, inspiration can be taken from nature, as biomimetic approaches can lead to functional and efficient results. Marine sponges present a porous and interconnected architecture and their efficient aquiferous system resemble the trabecular network of the bone tissue [10]. Furthermore, due to the spicules, some sponges have a rigid framework that grants them inherent toughness and stiffness, which are favorable mechanical properties for a bone tissue scaffold [12]. Naturally, the body architecture of sponges is clearly advantageous for bone tissue engineering. However, there are some hurdles to overcome, such as the fact that different sponge species possess different characteristics and compositions, being difficult to achieve reproducibility of the biomaterials and the animal supply must be sustainable and without disruptions [13].

This chapter will describe the state of the art of biomaterials inspired by the unique morphological structure of marine sponges and their potential for tissue engineering, highlighting their morphological organization, skeletal structures as spicules and efficient water-conducting system, as pore interconnected network enabling cell migration and proliferation across all the structure. The sponge skeleton has a simple to complex fibers network constituted by interesting variable biomacromolecules in different sponge species, as spongin and chitin. These biomacromolecules are being used as susceptible bioscaffold for promoting cell attachment, adhesion and proliferation and the latest developments on this route will be also addressed.

2.2 Marine Sponges as Outstanding Biomodel

2.2.1 Phylum Porifera

Sponges constitute the phylum Porifera (Metazoa), being the most primitive of multicellular and filter-feeding animals with an anatomically simple organization. This phylum is formed by mainly sessile metazoans and their aquatic members colonized a wide variety of habitats such as springs, falls, swamps, rivers and reefs but also the depths, from shallow to abyssal environments [14].

The sponges are considered representatives of the primordial multicellular animals and retain a combination of features that qualify as successful animal phylum [15, 16]. These animals have an important ecological role in marine ecosystem but sponges are also a potential source of novel bioactive compounds, synthesized by the interaction of sponges with symbiotic bacteria belonging to different phyla, providing new natural products and therapeutic drugs with perspective to improve the quality of human life [17–19].

In fact, most of the marine natural products in preclinical or clinical trials were obtained from marine invertebrates, predominantly sponges, tunicates, bryozoans or mollusks [20, 21]. Focusing in marine sponges models, sponges are typically difficult to maintain in aquaculture systems: beyond the requirement of large volumes of water that they usually filter, sponges in situation of poor water quality reduce their filtration rates, and consequently they showed a steady state decline in mean length in the few species that are possible to farm yet [22, 23]. Thus, a sustainable use of sponges is being investigated; however, the culture of sponge' cells remains a challenge as results from Muller and colleagues revealed that is harder to maintain a suspension culture of a single cell in laboratory conditions than sponge cells that have an organized tissue-like structure [24].

Commonly the skeleton and spicule structures of the marine sponges are the morphological structures used for taxonomic assignment. The classification into distinguishing taxonomical classes is based on the chemical composition of their skeleton/spicules. According to the Hooper and Van Soest, originally three classes of sponges were considered to their systematic classification [17]. Posteriorly, phylogenic study separated sponge species from Demospongiae class to a new class designed to Homoscleromorpha [25]. Actually, the classification of sponges are still controversial; however, it is majorly accepted the subdivision into four classification classes namely Hexactinellida, Demospongiae, Homoscleromorpha and Calcarea (Fig. 2.1) [26, 27]. The sponge members of each class may exhibit diverse morphologies, physiological and biochemical mechanisms that difficult their precise taxonomic classification.

Currently, the Porifera Phylum has registered 22,487 species subdivided by the four classes of marine sponge (Table 2.1). The most representative number of species is from Demospongiae class with 19,069 species according to World Porifera Database (WPD). Although, only 7394 sponge species were fully validated in Demospongiae class, which represents at least 61% unconfirmed identified sponges. These

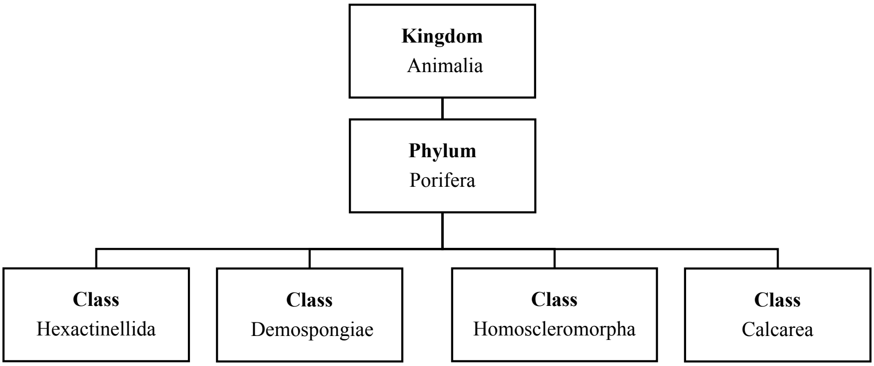

Fig. 2.1 Schematic taxonomic tree of sponges

Table 2.1 Number of all species and accepted marine species from each sponge classes and phylum according to WPD

	All species	Acc. species
Hexactinellida class	1536	633
Demospongiae class	19,069	7394
Homoscleromorpha class	171	109
Calcarea class	1700	740
Porifera phylum	22,487	8877

numbers appoint to the requirement of investigation and further insight in marine sponges' research .

2.2.2 Hierarchical Structures in Marine Sponges

Marine sponges display unique physiological features from nanoscale to the macroscale, as spicules and body networks, organizing in skeletons that are truly hierarchical structures with wide potentialities for various biotechnological purposes.

2.2.2.1 Marine Sponges Astounding Body Architecture Features

Marine sponges are metazoans animals which unique micro-architectural features are being a target of study by the scientific community. Sponges can have their body organized in radially symmetrical or asymmetrical architectures, taking into account their geometric shapes that can be calculate, tubular, arborescent, flabellate, globular or amorphous. In sponges, indeed, their morphological structures can display

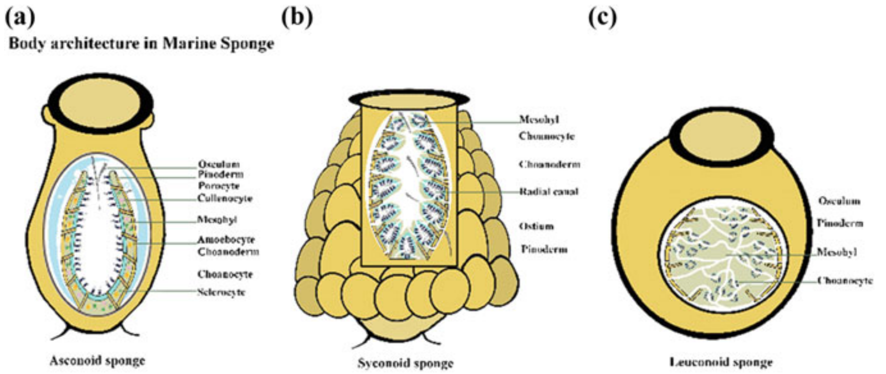

Fig. 2.2 Schematic representation of the types of body architecture and water-canal systems in Asconoid, Syconoid, and Leuconoid sponges

a variety of colors, sizes, cell types and structurally be organized in three distinct layers. The single outer layer of cells designed by the pinacoderm that separates the sponge from the external environment and contains a protein matrix with rove cells; the mesohyl inner cellular layer, and a layer containing the flagellated collar cells, the choanocytes [28]. In filter-feeding animals, the aquiferous system connected by an efficient network of water-conducting channels has an essential function and a simple type of structural organization. Furthermost, three types of sponge structure from the simple to complex regarding to the cells organization and water canal systems may be classified as asconoid, syconoid and leuconoid (Fig. 2.2) [29]. Thus, as previously mentioned, sponges may have branched shapes and distinct anatomical features accomplished by outstanding diverse skeletal structure organizations that enable their classification in different sponges classes (Table 2.2).

2.2.2.2 Skeletal and Spicules Structures Elements

The formation of skeletal features in sponges involves hierarchical mechanisms that secret organic fibers and mineral deposits. Initially, the organic molecules of skeletal structure are produced and then the deposition of inorganic elements occurs, yielding the small skeletal elements, the spicules [7]. Mostly, the sponge skeletons can be made by different elements as spongin (similar to the collagen protein), chitin, calcium carbonate and/or silica depending on the sponge' species that enclose an internal meshwork also formed by spicules elements produced by the scleroblast cells [17].

During the filtration process, these specialized cells sequester silica or calcium from the seawater and continue the biomineralization process for the production of the spicules skeletal elements in sponges. The microstructural diversity of these spicules is a well-connected structure with stylish design and numerous shapes. Moreover, spicules are morphological features present on mesohyl layer in sponges with

Table 2.2 Skeleton features are distinct in the four marine sponge classes of adapted from [17, 24, 30]

<table>
<tr><th>Hexactinellida</th><th>Demospongiae</th><th>Homoscleromorpha</th><th>Calcarea</th></tr>
<tr><td colspan="2">Skeletons are formed by amorphous, hydrated and non-crystalline silica</td><td>Skeleton has tetraxonic siliceous spicules without a subdivision in mega- and microscleres. The presence of spicules is a low number or even absent</td><td>Skeleton has calcareous spicules formed chiefly by calcium carbonate in crystalline forms (calcite, aragonite)</td></tr>
<tr><td>The skeletal elements are composed by siliceous spicules could be megascleres lengths. The class is known as a glass sponges due to their similar glass structure</td><td>Skeletal architecture is very diverse, made from siliceous spicules and protein (spongin) fibers or a combination of organic and inorganic elements</td><td></td><td></td></tr>
</table>

sizes from micrometers to centimeters (microscleres or megascleres) length [24, 28]. The spicule may precipitate from silicate salts creating the siliceous spicules or the spicules may precipitate from calcium and carbonate ions producing the calcareous spicules. Interestingly, spicules can have a highly variety of shapes for each sponge species that enables their identification [28]. The unique mechanical properties of biological structures as bone and sponge skeletons are a result of their competent design architectures. In *Euplectella* sp., within hexactinellid sponges also known as glass sponges, their skeletal elements comprise tree ring-like layers, which confer extraordinary biological properties [31]. Remarkably, the skeletons from *Euplectella* sp. have hierarchically arranged well-defined glass skeletons with an exceptional mechanical rigidity and stability properties, which is surely an interesting framework for fabrication of tissue engineering scaffolds and for various applications [32].

2.2.3 Components of Marine Sponges Skeletons

2.2.3.1 Biosilica

Sponges have the ability to synthesize enzymatically silicon dioxide (SiO_2), also known as biogenously formed polymeric silica (biosilica), to produce their siliceous skeleton and spicules, strong and flexible marine sponge skeletal elements, with highly complex structures and different levels of hierarchy from the nano to macro levels.

This biosilicification process occurs under their natural physiological conditions in aqueous media at near neutral pH and ambient temperatures, being biologically regulated. The biosilica organized deposition process is guided by a collagen organic matrix. Other biosilicifying organisms include diatoms (micro-alga), radiolarian and plants, although only sponges have the ability to polymerize silica generating large spicules. The silica-forming activity is usually high in sponge tissues, as exemplified by the demosponge *E. fluviatilis* which has an impressive spicule growth rate of about 1–10 μm/h^{-1} [33]. The silica element is the predominant inorganic component of the spicules in demosponges, but the incorporation of other elements, such as Na^+ and K^+, is possible to occur in the spicules [34]. In marine sponges, biosilica has the functions of serving as a structural support, providing protection from predators and acting as advanced sensors (e.g. biosilica as optical fibers) [32, 35].

The silicatein enzyme has proven to be very versatile, being involved in biomineralization and responsible for the formation of the siliceous spicules. Interestingly, the growth process of the spicules presents similarities to the bone formation mechanism: the central core rod of the spicule is first synthesized by a silicatein fiber, becoming surrounded by an organic silicatein layer, which will synthesize the second siliceous layer and so forth [36]. In both mechanisms, there is interplay of various factors that are functionally defined in a spatio-temporal context, so the studies on biomineralization must consider a series of well-tuned molecular pathways and interactions. Therefore, the elucidation of the biosilicification mechanism will allow the development of new materials and technologies for a broad range of biotechnological applications with significant impact, including the understanding of the formation of complex skeletal structures.

Regarding the calcareous sponges, the possible interaction of the carbonic anhydrase enzyme family in the formation of calcium carbonates to build calcitic spicules of the calcareous skeletons was described [30]. Interestingly, it was reported a highly hydrated amorphous network of silica in the demospongiae sponge *Tethya aurantia* [37] and a skeletal structure composed of elaborate cylindrical structures with six hierarchical levels was described in the hexactinellid sponge *Euplectella marshalli* [32].

Taking into consideration the biomimetic experiments inspired in marine organisms using, for example, recombinant carbonic anhydrase to form amorphous pat-like particles, it is evident that there was an improvement regarding our knowledge of the intricately basic functions and the chemistry of silica in the biomineralization process, which enables researchers to synthesize new materials [38, 39].

Cleary, biosilica and silica-based biomaterials are excellent biocompatible materials with enormous potential for biomedical applications in the areas of sensors, coatings, hybrid materials, biocatalysis and drug delivery, having particularly beneficial effects on bone and cartilage healing due to their capacity to increase mineralization (formation of mineralized calcium phosphate nodules or hydroxyapatite) [40]. For this reason, they are proper bone filling materials used to develop tissue-engineering scaffolds.

2.2.3.2 Polyphosphates

Polyphosphates (polyP) are inorganic polymers widely present in prokaryote and eukaryote animals, constituted by orthophosphate residues linked by high-energy phosphoanhydride bonds, having distinguishing functional properties [41]. This polymer present in the skeleton of marine sponges acts as an extracellular system for storage and delivery of metabolically useful energy, also having an active functional role in extracellular reactions of the bone biomineralization, providing a source of energy.

A study developed by Wang and colleagues evidenced that both biosilica and polyP inorganic polymers have a positive effect on the differentiation of human multipotent stromal cells (hMSC) in the different osteogenic or chondrogenic cell lineages. In fact, the gene expression of bone morphogenetic protein 2 (BMP-2) and alkaline phosphatase (ALP) was significantly increased by these polymers, mainly in the osteogenic cells. Additionally, both proteins were considered morphogenetically active additives as these are capable of upregulate the levels of collagen type I and type II transcripts, in osteogenic and chondrogenic cells, respectively [9]. Also, it was reported that the mineralization of osteoblast-like SaOS-2 cells is enhanced when the cells are exposed to the inorganic polymer polyP [42].

As demonstrated, polyP can be used in varied applications in the field of regenerative therapies of bone diseases and bone repair, with different biomedical purposes. Its utilization may be a useful tool for the development of novel bone biomimetic strategies [39].

2.2.3.3 Collagen and Spongin

Collagen is a ubiquitous protein with multiple functions in invertebrates and vertebrates, proven to be a versatile material with many applications in several fields as food industries, cosmetics, pharmaceutics, drug delivery, and tissue engineering. Collagen is the most abundant protein of the body, present on the extracellular cell matrix (ECM) of tissues including ligaments, skin, tendon and bone in human. In bone, this fibril protein is highly abundant and representing 90% of bone organic mass with importance in mineralization herewith calcium phosphates [43].

The extraction of collagen from marine sponges have been studied by different authors, developing methodologies that differ from the ones commonly used for mammals or fish, due to the supramolecular organization of collagens in marine sponges. In fact, acidic treatments are scarcely effective for the isolation of collagen from marine sponges, while the use of neutral to basic solutions, in the presence of chaotropic agents as urea and/or salts is being much more efficient, namely from marine sponges species known to be rich in collagen, as *Chondrosia reniformis*. The presence of collagen-like protein (spongin) in the skeletons of demosponges has been also a remarkable object of study.

Collagenous materials have been isolated from marine sponges as *Axinella cannabina* and *Suberites carnosus* [8]. In sponges, the compaction of collagen fibrils and filaments produce the spongin protein collagen, which has high porosity, thermostability, and mechanically rigid structures, being very handy for tissue bionics [44]. The spongin is a short-chain molecule that shares features with basement membrane collagen type IV [45] and the spongin organization has been reported as analogous to the human collagen type XIII [46]. Spongin was ascribed being more resistant to enzyme degradation than collagen [47]. Recently was reported the use of spongin-based scaffolds isolated from marine Demosponge *Hippospongia communis* as a 3D template for the hydrothermal deposition of crystalline titanium dioxide and also as a novel carrier for laccase immobilization for the removal of various bisphenols from water solutions [44, 47].

2.2.3.4 Chitin

Chitin is the second most abundant biopolymer (right after cellulose), being present in cell wall of some fungi but mostly on skeletal structures of arthropods, and mainly exploited from crustaceans shells, namely from shrimp and crabs. This biopolymer is thermostable, natural, non-toxic, biocompatible, and biodegradable with good mechanical properties. Chitin can be easily tailored for specific applications as drug delivery, wound healing, gene therapy and tissue engineering, enabling the development of nanoparticles, nanofibers, membranes, sponges, gels and scaffolds [48].

Interestingly, chitin is an integral component of skeletal structures of plenty invertebrates, including marine sponges. Chitin was found as a component of skeleton in sponges of the order Verongida in 2007 [49]. Recently, chitin has been reported and identified in the skeletal structures of four families of sponges related to the order Verongida (Demospongiae) and the *Farrea occa* glass sponge [7, 50]. Currently, the identification of α-chitin from the *Suberea clavata* demosponge of the Aplysinidae family may be a useful taxonomic tool for the identification of unknown demosponges species that possess chitin as a component of their skeletons [50]. Also, poriferan chitin may be a versatile template for fabrication of extreme biomimetic materials where high temperatures and pressures enable the development of remarkable bioinorganic composites with applications in water filtration, biosensing and regenerative medicine [51]. The skeleton of *Aplysina aerophoba* was used as an extreme biomimetic 3D-α-chitin scaffold material effectively mineralized under hydrothermal conditions (150 °C), using ammonium zirconium (IV) carbonate as a precursor of zirconia [52]. An example study of the sponge based chitin-scaffold showed exceptional properties such as diverse structural architectures, physico-chemical properties, ion absorption, great hydration and interconnected channels with different purposes toward biomedical applications, as mucoadhesive nature or anticancer, osteogenic and growth factor deliveries [48].

2.3 Biomaterials

Novel compounds isolated from marine species are increasingly sought, being a promising and inestimable source for the production of biomaterials for biomedical application, namely in regenerative medicine strategies. The classical approach counts on a design to provide architectural framework to potentiate cell growth and adhesion to the constructed scaffold, possibly in combination with other bioactive molecules, as cell growth factors, to ultimately promote the tissue regeneration.

At least a thousand marine sponges species and eleven sponge genera such as *Haliclona*, *Petrosia, Cryptotethia* and *Discodemia* have been studied and identified as source of bioactive secondary metabolites. Among these bioactive compounds, one can find potent tumor-inhibiting arabinosyl nucleoside, anti-cancer, anti-malarial and anti-inflammatory effects, with relevant biomedical application [2]. One can thus imagine the combination of bioactive compounds with structural macromolecules addressed in the previous sections for the development of functional biomaterials. Besides, recent advancement in biomaterials development and biofabrication is pushing the exploration of novel strategies on design of materials with biomimetic properties, i.e., learning from Nature unique strategies to inspire astonishing designs and/or introduce exquisite biological effects into therapeutic approaches. In this view, biomaterials inspired in marine species have been tailored, exploring not only the biological structures of marine sponges but also their chemical composition, aiming tissue remodeling towards bone regeneration [2, 53, 54]. Hence, sponge origin collagen has been used to develop and fabricate new biomaterials, benefiting from its properties such as low toxicity, biocompatibility and biodegradability Moreover, the basal spicules of hexactinellid sponges reveal a set of physiological features and optical properties as the size, durability, flexibility and triboluminescence, suitable for the development of new marine-derived biomaterials [48, 55]. These and other examples will be discussed in the following sections.

2.3.1 Bioceramics

Bioceramics are a large class of fully, partially or non-crystalline ceramics conceived for repair and reconstruction of injured parts of the body, having tremendous potential as biomaterials mainly for scaffolds tailoring. Bioceramics categories include the calcium phosphates (Ca/P) as hydroxyapatite (HAp), the bioactive glasses and the glass-ceramics. Based on their tissue response bioceramics can be classified as: nearly inert (e.g., alumina), bioactive (e.g., bioactive glass) or resorbable ceramics (e.g. α-tricalcium phosphate) [56].

This class of materials is primarily used in low- or non-load-bearing and in compressive load applications due to their particular mechanical properties. Their mechanical rigidity coupled with their inorganic nature makes bioceramics fitting for the repair and regeneration of hard tissues like bone and teeth, field in which these materials are employed for years [57].

However, inert bioceramics have some limitation caused by the formation of a fibrous capsule on the surface of the clinical implants, which prevents the bonding between the implant and the host tissue, thus hindering their use as suited scaffolds in the truly and fully repair of bone tissue, i.e., the integral regeneration of bone tissue. Contrarily, bioactive bioceramics are relevant to manufacture scaffolds for tissue engineering, revealing the capability of establishing bonds between the implant and the tissues, a critical step for the successful clinical treatments in regenerative medicine. In vitro and in vivo experiments revealed the formation of a layer of apatite in the glass surface responsible for bone bonding and repairing [57]: bioactive HAp or HAp-like coating layers are formed by a series of chemical reactions, supporting osteoblast cells adhesion, growth and mineralization, thus favouring bone tissue engineering strategies [58].

Furthermore, some bioceramics like HAp can be used for the development of permanent devices while others, such as some bioactive glasses, are degraded and reabsorbed by the body and their ionic dissolution products (e.g. soluble silica and calcium ions) can exert therapeutic effects like enhanced osteogenesis and induced angiogenesis [59–61]. In the latter case, scaffolds have the additional advantage of, if properly tuned, degrading at the same rate as the natural host tissue is replaced, leading to the total regeneration of the host tissue and the disappearance of the scaffold [6, 62]. In addition, bioactive glasses are also considered a promising application for stimulating the soft tissues' regeneration processes, including wound healing and angiogenesis mechanisms. The development of biomaterials for soft tissue engineering may benefit considerably from the bioresorbable features of some of these bioceramics [63].

Despite the recent advances in the field and the new technologies developed, mimicking the human bone porosity is still one of the main hurdles to overcome, due to the complexity of achieving suitable connectivity and tortuosity. Therefore, finding naturally occurring porous structures capable of being used as scaffolds or of providing templates for the production of innovative biomaterials is of utmost importance [64]. The employment of 3D structures from marine origin aiming for biomedical and biotechnological applications is not a new trend, as various animals have been used as 3D biomatrices in the last years such as sea urchins, coral skeletons and sponges [65, 66].

However, marine sponges remain overlooked regarding their bioceramics and the use of their body architecture as bioactive 3D bioceramics structures, when compared with other marine species [67–69]. Nevertheless, the use of marine sponges as precursors in the fabrication of ceramic-based scaffolds for bone tissue engineering has already been demonstrated [70, 71]. Using marine sponges as sacrificial templates for tissue engineering scaffold production is yielding very encouraging results, as the produced scaffolds preserve bioactivity, are non-cytotoxic, present adequate porosity and pore interconnectivity for cell proliferation and are able to achieve superior mechanical properties than the conventional bioactive glass scaffolds prepared with polyurethane [72]. Additionally, bioactive ceramics have the advantage of adsorbing and potentiating the role of growth factors and cellular ligands, a vital step toward tissue repair [73].

In fact, Cunningham and colleagues were able to produce tissue engineered bone scaffolds from the calcinated marine sponge *Spongia agaricina*, after submerging the specimens in an 80 wt% HAp solid loaded slip and drying them. The obtained Hap-based scaffold displayed an overall porosity of 56–61% with 83% of the pores ranging from 100 to 500 μm (average pore size 349 μm) and an interconnectivity of 99.92% [70]. In another study, performed by Boccardi et al., *Spongia lamella* and *S. agaricina* were used as sacrificial template materials. The marine sponges were immersed in PVA-water solution concentrated up to 40 wt%, dried, and immersed in bioactive glass powder and finally calcinated. The developed marine sponge scaffolds presented higher mechanical properties than those made by foam replica method due to a decrease in porosity (68–76%), without affecting pore interconnectivity (>99%). Noteworthy, the produced pore structure possesses pores with a diameter in the range of 150–500 μm, required for bone ingrowth, and also pores ranging from 0 to 200 μm, necessary for neovascularization, which are very difficult to obtain through artificial techniques [72].

In summary, even with new advances in the processing methods that allow to better control the 3D architecture of the scaffolds, employing the calcinated skeleton of marine sponges provides an exceptional 3D porous and interconnected structure directly and without further processing, while presenting an inimitable bioactive surface. Despite the promising results obtained so far, marine sponge bioceramics are yet to reach their full potential. Nevertheless, research in the area is continuing as marine sponge bioceramics present a promising future for tissue engineering. More will be discussed further on, when addressing the use of marine sponges as natural scaffolds.

2.3.2 Composites

A composite usually is produced using two or more compounds, which combined lead to the enhancement in the chemical, mechanical and physical properties of the final material. Hence, a proper composite is, for instance, a combination of hard and soft materials that balance the properties of toughness, strength and water content, having significant effects on the mechanical properties such as a better fatigue resistance and resiliency [74].

Likewise, hexactinellid sponges have spicules structures constituted by a hard material of hydrated silica and collagenous soft material that have highly flexible and tough characteristics [75]. Recently, research into biocomposites has been focusing in this class of marine sponges, more specifically in *Euplectella aspergillum*, *Hyalonema sieboldi* and *Hyalonema populiferum* species. These glass sponges represent an excellent biomimetic model to develop new inorganic-organic composite biomaterials inspired in the morphological, optical and mechanical features of their spicules [76]. In 2007, a silica-chitin composite biomaterial was tailored for the first time, mimicking the skeletons of the marine sponges [49]. Pallela et al. developed a tri-component scaffold system using marine origin biomaterials from the sponge *Ircinia fusca* (spongin/collagen) and the fish *Thunnus obesus* (chitosan and HAp) by freeze-drying (lyophilization) method. Comparison among chitosan, chitosan-HAp and chitosan-HAp-collagen scaffolds demonstrated that the tri-component scaffold had the highest thermal stability due to the presence of HAp and collagen, which are very stable. Furthermore, the developed scaffolds presented a higher in vitro cell proliferation using bone MG-63 cell line and an interconnected porosity (50–170 μm), proving to be an encouraging biomaterial for bone tissue engineering [77]. Arey and colleagues studied *Hyalonema* spicules and discovered that rigid natural composites, comprised primarily by a ceramic phase and containing an organic phase capable of fibril formation, would exhibit a viscoelastic behavior, contributing to mechanical energy dissipation, system function and survival to large deformations [78].

Therefore, it is clear that sponges represent an outstanding model for the biomimetic synthesis of 3D composites that present specific mechanical, optical and bioactive properties appropriate for the application as biomaterials.

2.3.3 Hydrogels

Hydrogels are three-dimensional polymeric networks made from hydrophilic, natural or synthetic polymers crosslinked by means of different mechanisms, rendering an insoluble polymeric matrix, capable to retain a large amount of water. This highly hydrated polymeric network constitutes an extensive framework for cellular proliferation, adhesion, and survival [79].

Indeed, hydrogels are biocompatible materials that mimic mainly the physical properties of soft tissue. These materials have many applications in regenerative medicine, namely tissue engineering, as well as on drug delivery [80], due to its flexible synthesis using different methods and an extensive range of components. They are based on synthetic polymers as poly(ethylene glycol) (PEG) [81] and poly(vinyl alcohol) (PVA) [82] or biopolymers and biomacromolecules such as collagen, agarose, alginate and chitosan (derivative of chitin) [83–86], among many others. Synthetic materials often have high toxicity in vivo and poor biodegradability and for these reasons, the biological polymers are more desirable over synthetic ones.

Collagen is itself a biomimetic material that has been used to the development of a vast number of biomaterials, as collagen-based hydrogels for tissue engineering. Although the main sources of collagen are still bovine and porcine skin and tendons, some ethical and religious concerns have been arising, namely the association to disease transmissions and potential immunogenic reactions [87]. Since the use of collagens for tissue engineering applications should be free of these type of issues, alternatives are being pursued and collagens isolated from marine organisms may be an alternative and sustainable option to be addressed [88], including from marine sponges as abovementioned. *Chondrosia reniformis*, a species of marine demosponge, consists predominantly of collagenous tissue that presents labile interfibrillar crosslinks, and this feature can be employed in many pharmaceutical and biomedical applications as injectable collagenous hydrogels [89].

Interestingly, different extraction methodologies to obtain the collagenous material have been reported in *C. reniformis*: the collagen/gelatin method using green solvents with water acidified with pressurized carbon dioxide [90, 91] and the novel method that extracts collagen/Glycosaminoglycans (GAG)-like molecules and other proteins, using a pre-treatment step with phosphate buffer saline/ethylenediaminetetraacetic (PBS/EDTA) and an incubation step with disaggregating solution, that yields a high collagen content with new rheological properties [89]. Nevertheless, the standard methodologies to produce collagen from this sponge species are based in chaotropic agents, as the ones developed by Swatschek et al. [92] or based on the method developed by Matsumura et al. for echinoderms [93]. This collagen can be used on the development of microparticles for drug delivery [94] or membranes for biomedical application [95]. Another study approaching cartilage tissue engineering suggested the incorporation on hydrogel in sponge architecture structure as strategy to increase structural stability and improve performance as scaffold [11].

2.3.4 Porous Marine Sponge as Natural Scaffold

The nanostructural organization of the body of the marine organism is an endless source of inspiration for offering multiple technical solutions in aerodynamics, bionics, architecture, and fabrication of biomaterials [96]. The body structure of marine sponges could be used as natural porous scaffolds that act as a support for the development of studies in replacement of bone and tissue engineering approaches. The skeletons of sponges are well-organized and functionalized structures with three-dimensional (3D) hierarchical architecture, adequate for the seed of human stem cells. These skeletons provide a support for the cells, but also an information to be used in the fabrication of synthetic tissue-engineering scaffolds, giving the biochemical cues provided by their composition [46].

Numerous studies have been undertaken to investigate the potential of marine sponges as natural scaffolds. According to Green et al. [46], the *Spongia* skeleton was used to be an affordable scaffold to test the hydration potential of spongin fiber network as an open porous fiber framework, which enables the human osteoprogenitor cells attachment, aggregation, and proliferation. Subsequently, histological examination showed the formation of the bone matrix. Results of the previous study confirmed the potential of sponge skeletons as a delivery scaffold for osteogenic factors and a sustainable source for bone tissue grafts and tissue regeneration [46].

Similarly, the potential of *Biemna fortis* marine sponges was studied as bioscaffold in bone tissue engineering and bone augmentation. The bare sponge scaffolds were produced by heating the specimen in a furnace at 1190 °C and further incorporation of two growth factors (IGF-1 and BMP-2). Results demonstrated that the skeleton of *B. fortis* showed a fibrous network with a 10–220 μm internetworked porosity [53]. Recently, a study with *Aplysina aerophoba* sponges as a 3D chitin-based scaffold demonstrated their potential use in tissue engineering. In in vitro assay study, the 3D biomaterials were cytocompatible and human mesenchymal stromal cells (hMSCs) attachment, growth and proliferation were confirmed by the increase of metabolic activity, cells number and differentiation into chondrogenic, adipogenic and osteogenic lineages [11]. This research revealed the potential of marine sponges as a scaffold and a novel source of chitin to be used in modern therapeutic tools for tissue engineering and biomedical purposes.

2.4 Biomedical Application

The marine environment is an exceptional source of new materials widely used for several biomedical applications due to their resemblance to the native extracellular matrix of human tissues and known safety origin to isolate compounds. The marine sponges in particular may be used as unconditional bioinspiration, as it is one of the most striking Nature models. As previously stated, the skeletons of marine sponges have high porosity and interconnectivity due to the presence of the canal systems, which provide a favorable environment for seeding osteogenic cell lines or hMSCs [11, 46]. These remarkable morphological structures can thus enable biomimetic approaches, especially for the fabrication of bone tissue grafts and regenerative therapies tackling bone diseases [53, 54].

Another inspiring feature of some marine sponges is the biosilicification process by which amorphous silica is generated from silicic acid esters by the silicatein enzyme, generating silica skeleton and spicules [97]. The controlled deposition of silica is of great potential importance in tissue engineering, as it would allow the modulation of the speed and amount of tissue regenerated during bone regeneration and tooth reconstruction in vivo and at mild physiological conditions. In order to possibly create via the biomimetic approach tailored biosilica structures the enzymes associated with this process, silicatein and silintaphin-1 and -2 (silicatein specific interactors), would have to be tightly controlled and balanced [98]. Wiens and collaborators, using recombinant silicatein and silintaphin-1 at equimolar concentrations, were able to produce biomimetic filamentous protein structures resembling natural axial filaments, establishing the basis to control in vitro biosilicification [99]. Furthermore, if the direct assembly of silica was controlled by the combined action of these enzymes and since spicules have the ability to transmit light efficiently [35], it would be possible to create micro-structured light-guiding composites that could be an economical substitute of industrial glass fibers. These composites can find applications in electronics and biosensors practical to the biomedical field. In an interesting work developed by Natalio and colleagues, an 8-Glu tag was added to the N-terminus of silicatein, conferring this protein HAp-binding capacity. The immobilized tagged proteins promoted the directed formation of biosilica coatings on synthetic HAp nanofibrils and dental HAp, after the addition of biosilica precursor [100]. This “smart glue” has the potential to seal surface defects, which would allow a reduction in the possibility of bone and tooth decay and of dental hypersensitivity, as well as to coat metallic implants with the intention of enhancing their biocompatibility or to encapsulate and release in controlled manner drugs or other bioactive compounds.

The presence of calcium carbonate ($CaCO_3$) in the spicules of some marine sponges is a noteworthy characteristic. Calcium carbonates are synthesized during the early hydroxyapatite-based bone formation and represent a component mineral in the matrix of the vertebrate bones. Also, the calcareous sponges own calcium carbonates skeletons where the inorganic elements, as spicules, are formed by means of an enzymatic reaction of carbonic anhydrase(s). Otherwise, in human, the bone mineralization mechanism is a highly regulated process and in case of flaw could promote the calcification in soft tissues (for example kidney stone formation), osteoporosis or dental dysplasia diseases, just to mention a few. The quinolinic acid sponge metabolite was capable of activating the carbonic anhydrase and enhance the mineralization of human bone cells [42], demonstrating that marine sponges can synthesize diverse metabolites with high applicability in human bone mineralization.

Nowadays, the demand for use of natural biodegradable materials has been growing in the scientific community and companies in the pharmaceutical field to take into consideration the requirement of highly innovative materials and technologies. The marine environment could be a viable and sustainable source of innovative biomaterials as the valorization of the marine species, like marine sponges, can be an alternative resource supply. Regarding the valorization of these resources, the natural skeleton of four marine sponge species was used as bio-based dressing in form of a powder or polymeric film shapes for drug delivery (L-cysteine hydrochloride) applications. Results pointed that the content of glycosaminoglycans (GAG) anchored in the skeleton of the natural sponge could act as bioactive-biomimetic carriers, regulating the wound healing mechanisms. This newly developed marine sponge natural biomaterial may be a sustainable alternative to the polymeric spongy-like matrices developed and available on the pharmaceutics market [101].

Demosponges, in association with microbes, are the major producers of pharmacologically important bioactive compounds. The novel leading compounds with clinical and pharmacological importance have been isolated from the symbionts actinobacteria living with marine species, and sponges-associated actinobacteria are the largest source of natural products with unusual biological activity [102]. Also, in a situation of nutrient competition and of a limited living space, the *Micromonospora* sp. marine bacteria associated with sponges could fabricate manzamines, a group of sponge-derived alkaloids. These compounds possess a high potentiality in the pharmacological field, with application in tuberculosis, HIV and malaria diseases [103]. Thus, the potential is huge and the story of marine sponges in the biomedical arena has just start to be written.

2.5 Future Remarks

The Ocean and marine resources are a source of widely unique natural products that display a wealth of biotechnological application, presenting a high potential for human health applications in the pharmaceutical and cosmetic industries, as well as in regenerative medicine, particularly when considering tissue-engineering approaches relying on the use of biomaterials. Indeed, the value of marine sponges as resources for new macromolecules and bioactive compounds is magnificent. The investigation of the micro-architectural and cell organization in sponges is central to tailor-made a biomimetic approach inspired by these important models and a sustainable alternative to the synthetic materials. The development of biomaterials inspired in natural models has a huge biomimetic potential, not yet completely explored. Therefore, it is required the improvement of our knowledge underlying the ecology, cell organization, reproductive biology, life spans and structural features of marine sponges. The research in marine sponges could prove to be useful on a number of fronts, either as a source of collagen for hydrogel production or as an additive to synthetic calcium phosphate or polymer scaffolds, as templates for producing biomimetic ceramic scaffolds or directly as osteoconductive grafts. However, these organisms present a significant drawback that is the sustainability aspect, due to ecological limitations (rare species and part of ecosystems that should be preserved, which is typically incompatible with harvesting) or technological constraints (sponges species are in depths that increase significantly the cost and requirements for their collection). A possible solution is the development of marine sponges farming techniques or the transplantation of sponges back into areas where they become extinct. Hence, sponges are promising species in which researchers continually attempt to improve or develop novel biomaterials.

To conclude, these biomaterials offer excellent and unique qualities like biocompatibility, degradability and promotion of cell adhesion, differentiation and proliferation. Advances in biomimetic materials research for tissue engineering should be inspired in Nature's materials as well as in marine structures since they were tested and developed for millions of years of evolution and present brilliant solutions and smart designs for our most complex challenges. Despite being ancient organisms, there is yet many blank pages on the book of marine sponges, but scientists across the world are cooperating actively to write some words and sentences. Ultimately, a story will come and their biomedical use will be a clinical reality.

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