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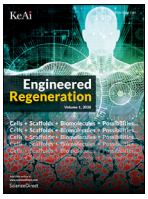

Metal-organic framework (MOF)-based biomaterials in bone tissue engineering

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Bone defects caused by congenital diseases, trauma, infection, tumors, or other factors are common orthopedic diseases, which affect the normal movement of patients significantly.[1] Clinical intervention is still required to achieve the complete healing and functional restoration. During that, the autologous or allogeneic bone grafts are the present gold standard treatment for large or severe bone damage, with about 2.2 million bone grafting operations being performed annually globally.[2] Although bone autografts usually produce satisfactory therapeutic effects, this approach results in increased complication, donor site morbidity and insufficient bone volume. And the use of bone allograft has other drawbacks that are associated with the risk of reduced graft bioactivity and poor integration with native tissue.[3] As alternative to achieve clinic need, bone tissue engineering is propounded in the 1990s as an independent area of research and has been rapid developed over the past few years. The historical methods for bone tissue engineering are using either biological or engineering techniques to produce tissue constructs. Instead, modern methods are toward using biomaterials to offer a biocompatible or even bioactive platform for tissue regeneration. Accordingly, the ideal bone tissue engineering material should have the following characteristics: (1) biocompatibility, defined as “the ability of a material to perform with an appropriate host response in a specific application”; (2) biological activity, facilitating either orthotopic or ectopic bone formation; (3) good mechanical and degradative properties to avoid the phenomenon of stress shielding; (4) interconnected aperture support structure, facilitating the seeding of osteoprogenitor cells, the infiltration of new blood vessels and perivascular nerve fibers.[3] With the development of material science, the types of bone tissue engineering materials are also increasing. In general, the most common biomaterials are polymers, bioceramics and composite materials. The major milestone schedule of the progress in the design of biomaterials for bone tissue engineering is shown in Fig. 1

As one important composite material, metal organic frameworks (MOFs), or coordination polymers (CPs) have attracted great consideration in the bone tissue engineering application. The term MOFs were named in 1995 by Prof. Omar Yaghi [4] and gained momentum in 1999 when MOFs were prepared as highly porous open frameworks.[5] MOFs are hybrid crystalline porous materials, formed by metal ions or clusters and organic linkers via coordination interaction. Therefore, their features can be easily achieved by adjusting the almost infinite combination of constructive components. Due to the unique physicochemical properties, including easy preparation and functionalization, tuned pore size, high surface area, variable structure and biocompatibility, MOFs have been thoroughly researched for application in various fields.[6] Recently, utilizing MOFs in biomedicine has become a rapidly developing hot research topic, especially nanoscale MOFs which are more flexible in applications, more readily endocytosed, have a higher potential for biodegradation, and can be more easily functionalized to meet desired host-guest interactions while maintaining a larger and tunable pore size. Since the first report on Cr-based MOFs (MIL-100 and MIL-101) for model drug ibuprofen delivery in 2006, multifunctional MOFs offered huge possibilities in the delivery of anti-cancer drugs and active regents (the enzyme, protein, DNA and RNA).[7] Sametime, MOFs material can act as the protective coating on fragile living organisms (viruses and cells) that protect them from external environmental during storage and transportation.[8] In addition, MOFs contain metal ions, for instance, Cu^{2+}, Zn^{2+}, Mg^{2+} as their structure blocks. These metal blocks are intrinsically involved in various biological process, such as wound healing, osteogenesis, and antibacterial properties. [9,10] These properties of MOFs endow MOF-based biomaterials as promising candidates for bone tissue engineering. Until now, the application focusing on MOF-induced bioactivity, including delivered and intrinsic bioactivity in bone regeneration, and performance improvement of repairing-related structure have been reported (Fig. 2).

In past few years, Ti implants with osteogenic drug dexamethasone (DEX) have been widely developed and applied as bone substitutes for defect repair. However, owning to some inherent defects, most of them are far from being satisfactory. To promote that, Ran and coworkers first encapsulated DEX into MOFs (zeolitic imidazolate framework-8, ZIF-8) and then immobilized DEX@ZIF-8 to micrometer-scale artificial etch pits on Ti substrate, followed by silk-fibroin membrane encapsulating (Fig 2a).[11] The present of ZIF-8 shell could endow the Ti implant

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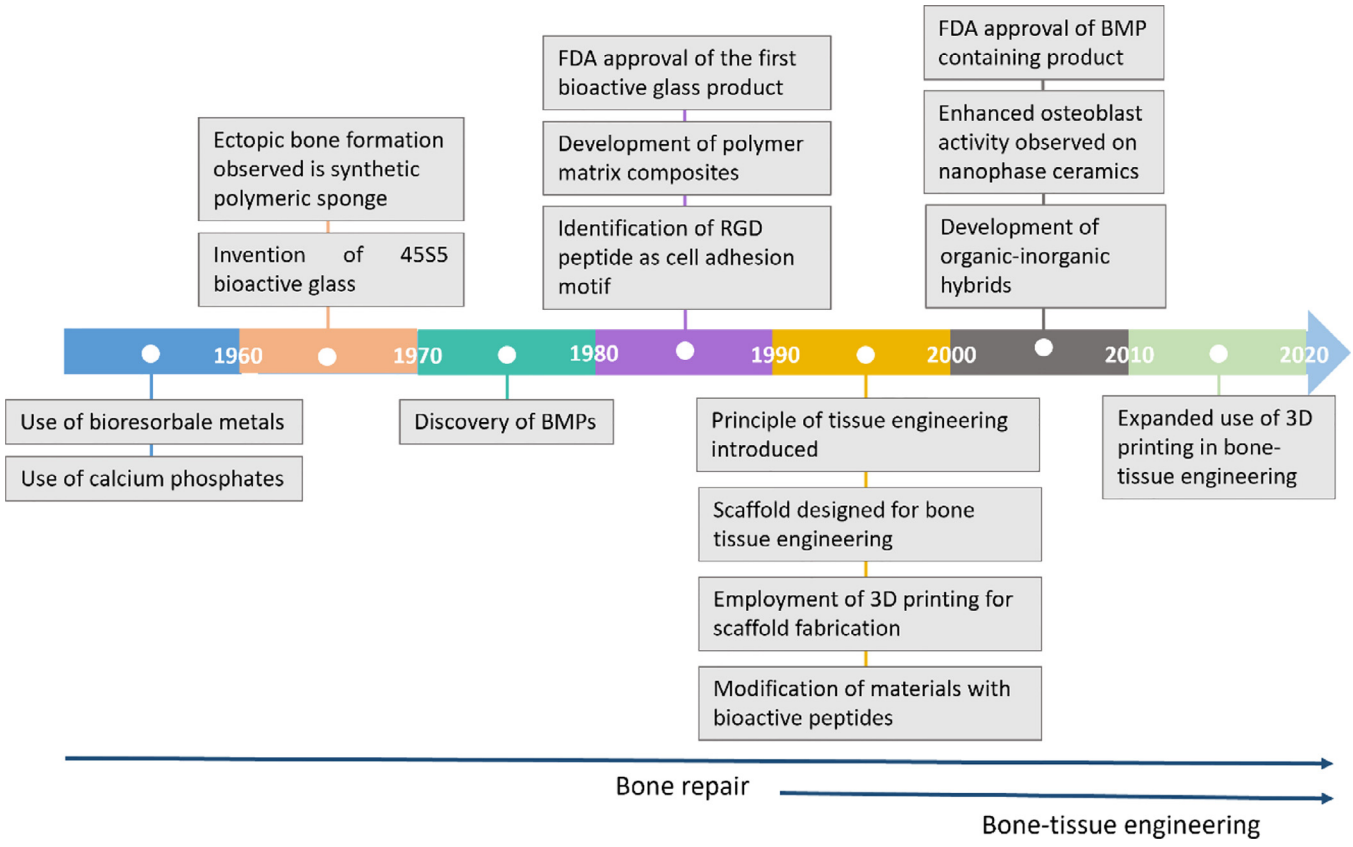

Fig. 1. Timeline of the major milestone for bone tissue engineering materials design. Adaptation according to [3].

to release DEX in a controlled and sustained way. *In vitro* cell culture on the prepared implant showed positive differentiation, calcium deposition and expression of osteogenic genes, implying its potential in bone regeneration. Similarly, MOF-embedded electrospin scaffold for BMP-6 effective carrying (98%) and controlled releasing (lasted up to 30 days) was developed by Toprak et. al. [12] The high encapsulation efficiency was achieved by one-pot crystallization of BMP-6 in MOFs. Compared with poly(Ɛ-caprolactone) (PCL) fibers only, MOF-embedded fibers had two-barrier BMP releasing pathway: escaping from MOFs and diffusing from PCL fibers. Both *in vitro* and *in vivo* studies shown marked effect of BMP-6 sustained releasing to osteogenic differentiation and new bone formation. Besides, MOF-based delivery scaffold has shown its powerful in tumor-induced bone defects. The highly tunable structures and biocompatibility of MOFs make them an ideal material for medical implants. While it is also a challenge to improve the physical integrity of MOFs in powder without compromising their chemical properties. The combination of 3D printing with MOFs is therefore used to produce composites with the mechanical strength of MOF infusion. This method is useful for generating in vitro models of tissue engineered grafts or bioengineered. [13] As shown in Fig. 2b, a nanoMOFs assembled 3D-printed scaffold was assembled and served as a delivery system that release anti-cancer drug (cisplatin) on demand to inhibit tumor growth and BMP-2 to promote osteogenesis. [14]

As compared to other nanomaterials, metal ions in MOFs´ central structure can be released on demand. These metal ions (referring to Zn^{2+}, Mg^{2+}, Ca^{2+} and Sr^{2+}) play an important role in osteogenesis, angiogenesis, and antibacterial process. The mechanism has been interpreted as that these metal ions can enhance alkaline phosphatase (ALP) activity, promote extracellular matrix mineralization and upregulate osteogenic gene expression.[9] Wan et. al proved that by modifying the electrospin asymmetric double-layer polycaprolactone/collagen membrane by MOF crystals (Fig. 2c).[15] The MOF crystals shown an ability of pH-responsive Zn^{2+} release, leading to enhanced osteogenesis *in vitro* and repairing of bone and blood vessels *in vivo*. More importantly, the angiogenic stimulation appeared only in the group having MOF crystals. When incorporating ZIF-8 into the 3D printed scaffold composed of polycaprolactone and dicalcium phosphate dihydrate, Zn^{2+} releasing was also achieved with a long-term benefit. This scaffold provided suitable templates for cell activities and enhanced bone formation. Inspired by that the simultaneous exist of Ca, Mg and Sr metal ions can result in bone regeneration, Little and coworkers prepared a MOFs structure taking Ca and Sr as structure metal ingredients (Fig. 2d).[16] The dissolved metal ions could induce proliferation and differentiation of hMSCs and MC3T3 cells.

Owing to their adsorption and conjunction ability to nucleic acid, proteins or peptides, MOFs materials have also been studied as cell culture substrates in bone tissue engineering. Accordingly, cell culture platform needs to have suitable surface properties for cell adhesion, proliferation and even differentiation. Ejeian and coworkers have grown ZIF-8 nanoparticles on polypropylene-modified membrane and utilized it for DPSCs proliferation (Fig. 2e).[17] Compared to conventional cells culture plates, the modified membrane caused an almost two-times growth in the primary attachment of DPSCs due to the increased roughness and higher surface area along with active base N atoms provided by ZIF-8 film. Further analysis also displayed the dramatically overexpression of osteogenic markers (Bone Sialoprotein-1 (BSP-1) and BMP-2) and the formation of 3D cartilage-like structure. Therefore, this MOFs´ modified membrane exhibits profound capacity as a prospect nano-medical instrument in guided bone regeneration (GBR). Excellent performance of MOFs´ nanostructures provide a material-based substitute to cellular microenvironments. Besides, MOFs can also be used as a potential additive to improve the mechanical properties of hydrogels in bone grafts. For example, Liu et al. successfully functionalized CA-CS hydrogels with ZIF-8 nanoparticles as biofunctional adhesive (Fig. 2f).[18] Series of re-

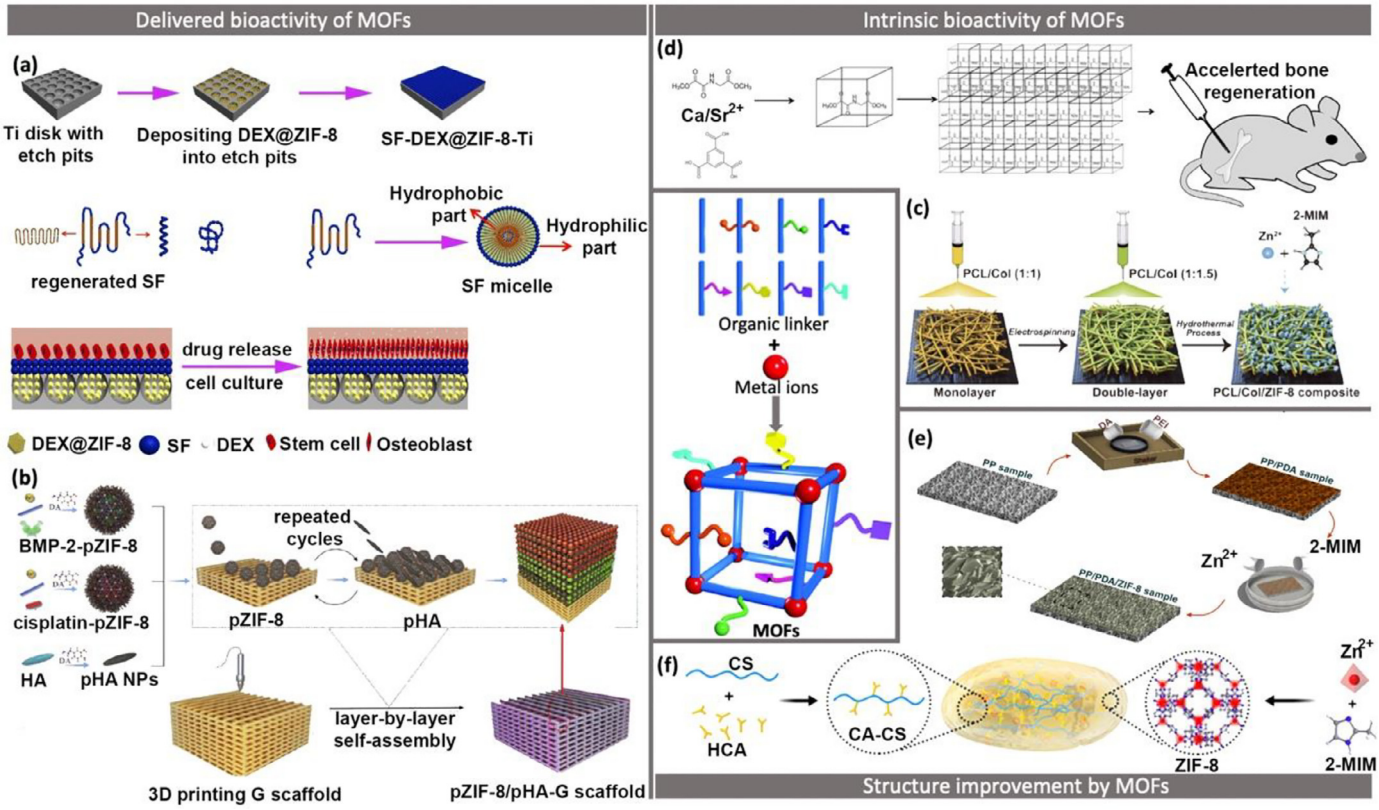

Fig. 2. MOFs-based biomaterials in the application of bone tissue engineering: (a) preparation of DEX@ZIF-8 immobilized titanium (Ti) substrate (Copyright 2017, Elsevier); (b) preparation of nanoMOFs assembled 3D-printed scaffold for cisplatin and bone morphogenetic protein-2 (BMP-2) delivery (Copyright 2021, Elsevier); (c) fabrication of ZIF-8 modified electrosin asymmetric double-layer polycarolactone/collagen membrane (Copyright 2021, Wiley-VCH GmbH); (d) preparation of CaSr-MOFs for bone regeneration (Under the license of CC BY); (e) presentation of MOFs-modified substrate for dental pulp stem cells (DPSCs) proliferation (Under the license of CC BY-NC); (f) preparation of ZIF-8 modified catechol-chitosan (CA-CS) hydrogels with ZIF-8 nanoparticles as biofunctional adhesive (Copyright 2020, American Chemical Society).

sults verified the addition of ZIFs in the hydrogel greatly increased its crosslink density and mechanical strength due to the chelation of catechol groups in hydrogel and Zn^{2+} in ZIF-8. The interface between ZIF-8 nanoparticles and CA-CS polymer matrix played important role in this process. Benefiting from this, the ZIF-8 modified hydrogels performed more credible in adhesive test and prevented the loss of bone grafts *in vivo* efficiently. This strategy is a promising method to solve the problem of poor bone regeneration due to the bone graft loss and inadequate fixation.

Taken together, numerous advanced MOF-based platforms have been developed to meet the requirements in bone tissue engineering. Bioactive agents´ delivery, intrinsic metal ions releasing and implanted scaffold improving endow MOFs to realize their great potential in the positive bone repair outcome. Compared with bioactive inorganic materials (bioactive ceramics, bioactive glasses, tricalcium phosphate and their combinations), MOFs can act as nanocarrier and have less brittle nature. Compared with polymers (collagen, hyaluronic acid, polylactic acid, polyglycolic acid and their copolymers), MOFs have s certain mechanical strength and interconnected aperture support structure. MOFs biomaterial, combining the toughness of a polymer phase and the compressive strength of inorganic one can go beyond other materials and shed new light on bone tissue engineering. Combining 3D printing and MOFs to manufacture high-quality bone repair materials should be another potential application. But before that, more efforts are required to understand the degradation mechanisms and pathway of MOFs *in vivo*. Due to the different functions to different MOFs, their clearance and basic dose responsive of individual tissues are also challenges that need to be addressed. In addition, the toxicity of MOFs with different compositions, structures and morphologies should be taken into consideration. This is essential for MOFs-based biomaterials to achieve improving treatment outcomes in bone tissue engineering.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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