Review

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High-throughput screening for integrative biomaterials design: exploring advances and new trends

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With the increasing need for biomaterials and tissue engineering alternatives, more accurate, rapid, and cost-saving methods and models to study biomaterial–cell interactions must be developed. We review the evolution of microarray platforms used for such studies in order to meet the criteria of complex tissue engineering biological environments. Particular aspects regarding biomaterials processing, data acquisition, and treatment are addressed. Apart from *in vitro* array-based strategies, we also address emerging *in vivo* high-throughput approaches and their associated trends, such as the role of inflammation in regeneration. The up-scaling of high-throughput methods using single cell encapsulation systems is also explored. Possible limitations related to the use of such methods, such as spot-to-spot crosstalk, are also discussed.

High-throughput analysis for biomaterials development

The challenges associated with life quality maintenance in ageing populations require better biomaterials, particularly in the field of tissue engineering. However, the development of new materials designed to address specific biological problems is hampered by multiple complex factors associated with their application, including materials chemistry, topography, cell–protein interactions, cell types, and physiological state (Box 1). Rapid cost-saving testing of biomaterial–cell interactions is needed to understand the complexity affecting this area [1,2]. Moreover, efforts to design more truthful biomimetic cell niches are needed [3–6] because conditions used *in vitro* are still fairly distant from mimicking the body environment, particularly at the cellular level.

In this review, we focus on the advances in the design of biomaterial arrays that are compatible with cell/drug encapsulation, miniaturization of porous scaffolds, and adaptation with mini-/micro-bioreactors (Table 1). The dependence of automated equipment for the patterning of biomaterials/cells in the platforms used for high-throughput screening (HTS) will be compared with techniques that allow for bench-top dispensing of biomaterials [7–9]. A recent trend consisting of the implantation of biomaterial arrays in animal models will also be explored (Figure 1) [10]. Single cell encapsulation in biomaterial microparticles will also be addressed, as it is fast becoming an easily up-scalable method for the study of biomaterials [11].

Evolution of high-throughput systems for biomaterials screening: finding inspiration to solve current needs

The perspective of a rapid, efficient, and industry-paced discovery of adequate materials for implantation was implemented with the development of miniaturized biomaterials arrays [12,13]. Such systems have seen significant development during the last decade to meet the specific needs of the evolving biomaterials field, where the importance of reproducing biological niche-like 3D environments [14] and the effect of several external parameters affecting biological response were reported [15–18]. In this section, we present a critical report on the developments of biomaterials HTS systems.

Direct writing techniques

The first biomaterial microarray was suggested in 2004 by Anderson *et al.* [13]. It consisted of over 1700 contact-printed and polymerized monomers onto which ESCs were seeded. Relevant and unexpected effects of materials on cell proliferation and differentiation were identified on chips the size of a microscopy glass slide. Contact printing uses pins to dispense a material volume, whose deposition occurs after direct contact with the surface, which has previously treated to prevent cell adhesion. Material size and shape is determined by the pin size [19]. Such a technique allowed for the rapid mapping of interactions between biodegradable polymeric biomaterials, proteins, and stem cells [20,21]. The stiffness of more than 1700 biodegradable biomaterials was also characterized by nanoindentation in a few days [22]. Hook *et al.* identified biomaterials formulations that reduced the attachment of pathogenic bacteria and validated such results by implanting 'hit' biomaterial-coated silicone in mice [23]. Contact printing was recently used to print photopolymerizable hydrogels containing encapsulated cells,

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followed by analysis of their osteogenic potential totally on-chip [24].

Inkjet printing developed as a non-contact direct writing printing technique (Table 2). It was used to pattern hydrogels, proteins, and cells in the form of miniaturized arrays [25–28]. It is performed by ejecting nanoliter volumes of solutions from a microcapillary onto specified surface positions. Piezoelectric stimuli or heat may be applied in order to separate the liquid from the tip of the nozzle; the use of the heating strategy allowed cell encapsulation with viability in the range of 90% [29]. Alternatively, laser printing (Table 2), as firstly suggested by Guillemot *et al.* [30], was used to print microarrays of cells – avoiding DNA fragmentation [31,32] – ceramic/polymeric biomaterials, and proteins [33].

Indirect writing techniques

Indirect writing techniques require the pre-production of a template to pattern biomaterials and mixtures thereof [34]. In photolithography (Table 2), a substrate is irradiated with high energy through a photo-mask. Surface alterations can include the ablation of a photoresistant layer, initialization of polymerization, or surface modification. Yuan *et al.* [35] developed a method for patterning and studying the migration of different types of cells on substrates composed of different materials with flat features or with grooves. Poly(ethylene glycol)-diacrylate (PEG-DA) microwells produced by photolithography [36] were used as reservoirs to study biomaterial–stem cell interactions after depositing biomaterials in the microwells by contact printing [37].

In soft lithography, an elastomer – usually polydimethylsiloxane (PDMS) – is applied in a pre-designed mold and further crosslinked, possessing a pattern that corresponds with the negative of the template. Moraes *et al.* produced a microfabricated platform for unconfined compression of biomaterial arrays by soft lithography (Table 1) to study its effect on encapsulated mesenchymal stem cells [38].

The particular case of wettability contrast-based arrays

Superhydrophobic surfaces patterned with wettable regions are a particular type of indirect writing platform used for biomaterials studies. It is generally accepted that superhydrophobic surfaces show water contact angles higher than 150° and low surface energy, effectively repelling water adhesion [39]. In such surfaces, biomaterials remain restricted to the wettable spots due to the wettability contrast between them and the superhydrophobic surrounds [7,40,41]. This approach allows patterning of water-based biomaterials with distinct shapes and heights, depending on the shape and area of the wettable spot, as well as on the volume dispensed (Figure 1A). It was shown that cell attachment or proliferation is avoided in the superhydrophobic parts of the chips [42–44].

Protein–cell interactions were studied in independent spots of polystyrene chips, avoiding the contamination or crosstalk of neighboring spots with factors released from the cells or materials present in neighboring spots [41]. Using polystyrene chips, biomaterials were dispensed in wettable spots by pipetting [45–47]. Nonetheless, the total flatness of the platforms makes them compatible with any automated printing strategy. Hydrogels with encapsulated cells were also patterned and analyzed by image-based techniques (Table 2) [45]. Porous scaffolds were also processed in the form of miniaturized arrays (Figure 1A) for the first time in a platform compatible with the minimum size required for a scaffold with a representative number of pores [46]. These platforms also allow for direct access to the biomaterial constructs, because these are not confined by walls. This feature enabled on-chip porosity assessment and unconfined dynamic mechanical analysis of the structures using *in situ* and non-destructive techniques to be performed [46,47].

Levkin and coworkers proposed a superhydrophilic surface patterned with superhydrophobic borders comprising 2-hydroxyethyl methacrylate-co-ethylene dimethacrylate (HEMA–EDMA) photopatterned with poly(2,2,3,3,3-pentafluoropropyl methacrylate (PFPMA) through a photo-mask.

Box 1. Complexity of biomaterials development for tissue regeneration or substitution strategies

Tissue regeneration is mediated by the cellular response, affected by the environment created by biomaterials and delivered molecules, and stimulation of the whole tissue by, for example, mechanical means. The complex choice of a biomaterial for organ substitution or regeneration is decided after evaluating the type of damage and its dimensions. The final goal is having a biomaterial that, alone or in combination with other factors such as bioactive molecules and with specific cells, modulates cell and tissue responses to achieve full regeneration (Figure I).

Depending on the defect, materials in the form of coatings/membranes (isotropic or with gradients), 3D scaffolds, or cell-laden hydrogels may be chosen. Biomaterials can be processed from several types of components: metallic, polymeric, ceramic, composite, and self-assembled low molecular weight molecules, among others. A wide range of techniques is available to process such materials, for example, solvent casting, layer-by-layer methods, photopolymerization, ionic gelation, and rapid prototyping. The origin, composition, and processing of the biomaterial will determine its physicochemical characteristics, such as topography, wettability, protein adsorption profile, mechanical properties, viscoelasticity, soluble factor uptake/release, and degradability. Some of these characteristics will vary in time after implantation with mechanical and chemical stimuli, for example, as a result of the mechanisms of degradation that may occur by action of cells.

Implanted biomaterials may contain seeded or encapsulated cells – of autologous or allogenic origin – and bioactive molecules. Such cells may be of primary lineage, stem cells derived from different origins (e.g., adipose tissue, bone marrow), or induced pluripotent stem cells. Stem cells may be implanted in a native post-retrieval state or at different stages for pre-differentiation *in vitro*. It is also well known that in some biological tissues, such as osteochondral tissue where there is an interaction between chondrocytes and osteoblasts, the presence of co-cultures may be important to promote natural-occurring interactions.

For biomaterials loaded with bioactive molecules, their release must be controlled so that they induce the desired response in cells. Such molecules may consist of growth factors to promote cell differentiation, molecules for surface modification of biomaterials, or genetic material to be delivered intracellularly to tailor the fate of a cell.

The study of cell response must be studied *in vitro* – either with mechanical stimuli that mimic the organism action or in static environment. This process must be optimized until promising results are achieved. Selected conditions must be tested in animal models, firstly for initial response studies (e.g., inflammatory response) and later for tissue regeneration.

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