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Multi-scale adaptions of dynamic bio-interfaces

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ABSTRACT

Biodevices including wearable sensors, medical implants or protheses (*e.g.*, tissue engineering scaffolds and neural electrodes), have attracted extensive attentions over the past several decades due to their great potentials in multiple areas of healthcare, diagnostics, and rehabilitation. The performances and efficiency of biodevice-tissue integration and adaption are significantly affected by their bio-interfaces, which should be therefore carefully considered and optimized. This perspective briefly summarizes the emerging biodevices with bio-inspired dynamic bio-interfaces for accommodating the dynamic natures of cell functions or human body tissues on molecular-, nano-/micro-, and macro-scales, which hold promises to bring in breakthroughs to some future technologies such as personalized medicine, artificial organs, and human-machine interaction and integration.

With remarkable progresses of wearable and implantable biodevices in recent two decades, some technologies of human-machine interaction and integration once existing in scientific fictions have been coming true. For example, assisted by a variety of wearable and implantable biodevices, we can monitor physio-pathologically relevant signs in a real-time manner through wearable and implantable flexible sensors, modulate animal's behaviors, feeling and cognition through brain-machine interfaces, and restore vision for blind patients through implantable retinal prosthesis. It can be witnessed that various fields of diagnostics and therapy are being revolutionized by emerging advanced biodevices. However, with increasing demands of wearable and implantable biodevices enabling seamless integration with human body tissues for long-term stability and reliability, the conflicts between less adaptative capabilities of biodevices and dynamic natures of human body tissues have become prominent. Given the contact and interactions between biodevices and biological tissues/cells take place at bio-interfaces, improved compliance of man-made biodevices to tissues in partially or all aspects of their dynamic mechanics and geometries therefore requires the bio-interfaces to be also dynamic for adapting to targeted tissues. In the human body, cell-cell communications and tissue interfaces are fulfilled by multi-scale strategies, such as bioactive molecules, nano/micro-topographical cues, and tissue biomechanics. It is therefore of great importance to design and develop dynamic bio-interfaces mimicking the native bio-interactions in multi-scale manners for achieving enhanced bio-adaptive outcomes. Under this biomimetic principle, some attractive biodevices with elaborately designed dynamic bio-interfaces have recently been investigated and developed, particularly emerging on basis of recent advances in stimuli-responsive polymers, showing interesting promises in accommodating the mechanics and geometries of host tissues and therefore endowing the biodevices with superior performances and functions.

1. Molecular-scale bio-adaption

On the molecular scale, molecular binding of various biomolecules via membrane proteins at cell surfaces, typically through specific ligand recognition, plays a vital role in determining cell-cell communications and cell-matrix interactions in the human body. For example, a variety of cell functions such as cell adhesion, migration, proliferation, and differentiation can be modulated by Arg-Gly-Asp (RGD) peptide sequences via mediating integrin binding and matrix metalloproteinase (MMP)-sensitive degradation and specific growth factors that induce certain cell response. There have been long-standing trials in functionalizing biodevices with biomolecules by typical means of incorporating bioactive growth factors or grafting RGD peptide sequences for engineering biocompatible or/and bioactive bio-interfaces. However, for any specific physiological processes, there are extremely high spatiotemporal complexities in the activations of variety types of biological signals. Despite some advances in improving the biocompatibility and bioactivity of biodevices by engineering bio-interfaces via biomolecules, it shall be greatly challenging, if any possible, to construct bio-interfaces with the incorporations of multiple biomolecules and to precisely control their releases one by one in specific spatiotemporal manners recapitulating or mimicking the situations in the human body. To address the conflict

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between the high complexity in biomolecular demands in the human body and the limited controllability of existing methods for controlling the releases of biomolecules, directly incorporating living cells that can produce multiple biomolecules responding to cell microenvironments has offered a promising strategy. Under this strategy, living platelets were incorporated within bio-printed hydrogel nerve conduits made of gelatin methacrylate (GelMA) and poly(ethylene glycol) diacrylate (PEGDA). Thanks to the capabilities of the incorporated living platelets that secret multiple growth factors responding to the regenerative microenvironments of the peripheral nerve (Fig. 1), the nerve conduits with engineered bio-interfaces containing living cells achieved desirable outcomes in repairing a large gap (1 cm) of sciatic nerve injury [1]. With the assistance of living cells, the biodevices with the bio-integrated living interfaces will be promising to meet the requirements of dynamic administration of multiple biomolecules. However, even for the bio-integrated living interfaces, controlling or enhancing the secretions of multiple biomolecules adaptative to different stages of specific physiological processes are still challengeable, which shall be an important direction for future investigations.

2. Nano/microscale bio-adaption

On the nano/microscale, the mediations through nano-/micro-topographical cues of extracellular matrix (ECM) are important approaches for determining cell geometries and subsequently a variety of cell functions such as focal adhesion, migration, proliferation, and differentiations via mechanotransduction signaling. Constructing biodevices with specific nano/micro-topographies mimicking those of ECM can also affect cell mechanics and functions, whereas conventional ones with static nano/micro-topographies lack the capabilities of dynamic cell manipulation in a specific temporal manner. Inspired by dynamic natures of ECM on nano/microscales at different stages of vascular tissue regeneration, we have designed and developed dynamic bio-interfaces with changeable nano/micro-topographies for mimicking the functions of native ECM [2]. Using a biodegradable and biocompatible shape-memory polymer, poly(*L*-lactide-*co-D, L*-lactide), to form the bio-interface, their nano/micro-topographies could be remotely tuned by near-infrared (NIR) light accordingly from initially anisotropic to later isotropic. This dynamic bio-interface with two tunable nano/micro-topographies meets the distinctly different requirements of cell modulation at different stages of endothelialization throughout the vascular regeneration process (Fig. 1), *i.e.*, firstly directing endothelial cell migration and then promoting the formation of intercellular junctions among vascular endothelial cells to be a confluent endothelial cell monolayer. Benefited from their possessing appropriately engineered nano/micro-topographies, biodevices with dynamic bio-interfaces have shown the "intelligence" of better interaction and functional adaption with targeted tissues. It is also very interesting that the bio-interfaces with appropriately engineered nano/micro-topographies could even modulate the foreign body response of medical implants. No matter what types of synthetic and nature-derived materials are used to form biodevices, the integration, particularly implantation, of biodevices in the human body always evokes the immune system and causes inevitable foreign body responses, which significantly impair the performances and functions of the implants yet lack effective strategies for addressing it till now. Recently, we found that neural electrodes with bio-interfaces of microcone array topographies could reduce the recruitment of inflammatory glial cells yet promote the neurite outgrowth and connections of neurons [3]. With increasing understanding and knowledge about the underlying mechanism that how the nano/micro-topographies of bio-interfaces affect specific cell functions and foreign body response, it will be greatly promising to realize enhanced functional adaptions of

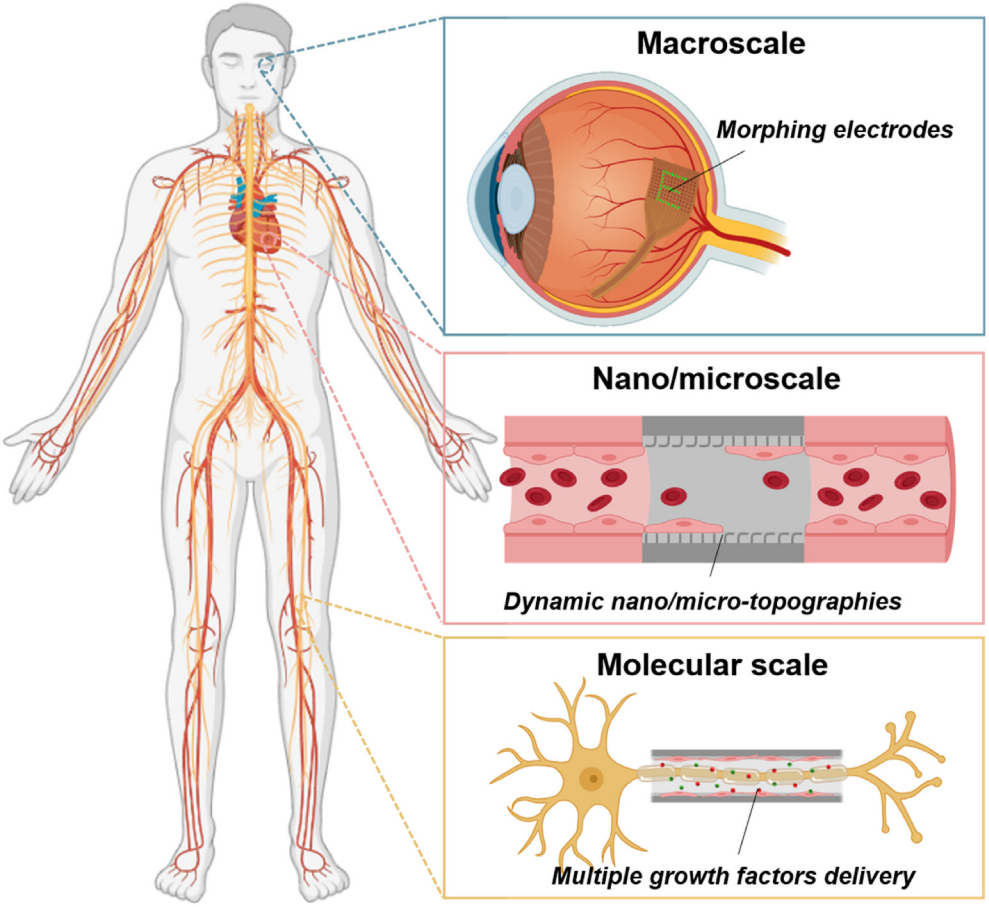

Fig. 1. Biodevices with dynamic bio-interfaces for multi-scale adaptions and diverse biomedical applications, including nerve conduits with dynamic bio-interfaces containing living platelets for secreting multiple growth factors, adaptive to the peripheral nerve tissue regeneration on the molecular scale, vascular grafts with dynamic bio-interfaces of tunable nano-/micro-topographies, adaptive to dynamic manipulation of endothelial cells throughout endothelialization on the nano/microscale, and morphing retinal electrodes adaptative to the curved shapes of eye on the macroscale.

biodevices through designing dynamic bio-interfaces with controllable nano/micro-topographies.

3. Macroscale bio-adaption

On the macroscale, the mismatch between the biodevice and human body tissues is one of the most prominent problems impairing the performances and functional fulfillments of wearable and implantable biodevices. In general, the mismatches are represented in mechanics and/or geometry. Unlike biodevices made of synthetic materials usually showing linear elasticity/plasticity (such as homogeneous elastomers) or simple rigidity (such as metallic materials), human body tissues exhibit complicated viscoelasticity upon mechanical loading and deformation [4], *i.e.*, firstly instantaneous elastic response with a storage modulus like elastic solids and then slow shape recovery and energy dissipation or loss with a loss modulus like viscous liquids. Though the biodevices with body matrix made of elastomers can mimic the soft nature and elastic moduli of human body tissues to some extents, their inherent differences in mechanical properties still bring in inevitable conflicts in mechanics between biodevices and tissues. When shaping an elastic biodevice to accommodate the host tissues via deformation, the stored high energy of the biodevice may cause excessive compression or even stress-induced damage of tissues owing to the mechanical mismatch. To design biodevices with tissue-like viscoelastic bio-interfaces is of great significance for addressing the challenge. Viscoelastic hydrogels are excellent candidates for forming the bio-interfaces enabling mechanical adaption to soft tissues. Recently, a submillimeter-scale ferromagnetic soft continuum robot was developed [5]. The friction between the robot and soft tissue could be effectively minimized by coating a hydrogel skin on the robot to engineer a mechanically adaptable bio-interface mimicking the viscoelasticity of body tissues. The risks of damage to tissues during the steering and navigation of the robot within small cavities or lumens of tissues were therefore significantly reduced, endowing the potentials in biopsy or endoscopic surgery in hard-to-reach areas of human body. In addition, mechanically adaptable bio-interfaces could even make biodevices adaptative to dynamic processes of a specific physio-pathological process. For restoring heart functions after myocardial infraction, a cardiac patch made of ionically crosslinked starch hydrogel with viscoplastic properties has been studied and developed [6]. As an interesting subset of viscoelastic materials, viscoplastic materials exhibit viscoelasticity when the loading or deformations below the “yield stress”, yet plasticity, *i.e.*, permanent deformation, when the applied stress exceeds it. Due to its excellent viscoplastic properties, the ionically crosslinked starch hydrogel cardiac patch exhibits a dynamic bio-interface with changeable moduli and stress-relaxation behaviors in response to the frequency of strain, which can effectively resist pathologic left ventricular dilation and remodeling owing to its plasticity yet bring minimal restrains on the beating of normal heart tissues owing to its viscoelasticity at the frequency of oscillation near the range of heart beating.

As for addressing the geometrical mismatch between biodevices and body tissues, dynamically controlling the shapes of bio-interfaces for accommodating the curved surfaces of three-dimensional (3D) body tissues has offered promising strategies. Usually, biodevices are initially two-dimensional (2D) flat shapes for the eases of manufacturing and processing, which needed to be deformed to designated curved shapes for the geometrical compliance to curved body tissues. Using programmable deformation strategies, we successfully prepared conformal electrodes adaptive to curved shapes of nerve tissues and eyes [7,8], realizing close contact between the implanted electrodes and the curved tissues for potentially reliable and high-efficiency nerve stimulation (Fig. 1). Additionally, we also developed a shape-morphing vascular tissue engineering scaffold [9], which achieved not only desirable shape adaption to 3D tubular blood vessel but also rapid 3D endothelialization through the high-efficiency 2D cell incorporation and subsequently programmable folding of the cell-incorporated scaffold at the physiological temperature (37 °C). However, the deformations of a flat-shaped biodevice via simply bending, folding, or twisting can only result in curved shapes with zero Gaussian curvatures, which remains different compared to human body tissues usually possessing complicated non-zero Gaussian curvatures. To address this challenge, responsive hydrogels with precisely controlled in-plane differential swelling behaviors have offered promising strategies. By mimicking the principle of the morphogenesis and growth of natural 3D tissues, a poly(*N*-isopropyl acrylamide) (PNIPAm) hydrogel film with spatially different crosslinking degrees encoded via digital light printing was prepared [10], which could be deformed to any targeted shapes with complicated non-zero Gaussian curvatures such as human's face through the differential in-plane swelling of different regions. This study offered a robust and universal strategy for accurately creating a 3D structure with tissue-like complicated non-zero Gaussian curvatures from a 2D flat shape, which will inspire the design of biodevices with controllable shape-changing bio-interfaces enabling active compliance to curved 3D tissues. Nevertheless, even for biodevices with 2D-to-3D shape-changing bio-interfaces, their shapes are hard to be further dynamically tuned within a wide range upon integration within the human body, resulting in great difficulties in accommodating changing shapes of growing tissues. Recently, a viscoplastic material, a modified poly(dimethylsiloxane), was introduced in the bio-interfaces of a neural electrode, which could be deformed via non-stress passive compliance and adaptive to growing nerve tissues owing to their excellent viscoplastic behaviors [11]. With the viscoplastic bio-interfaces, the neural electrode desirably accommodated the suddenly changing shapes of nerves during the compression and motion of tissues (contributed by the viscoelasticity of the material at a high rate of strain). Additionally, it could also adapt to the slow volumetric expansion of growing nerve tissues with yet without generating any mechanical constraints through the passive compliance of the morphing device to the growing tissues (contributed by the plasticity of the material at a low rate of strain showing nearly zero stress). The biodevices with dynamic bio-interfaces on macroscale simultaneously meeting the adaptive requirements of both mechanics and geometry have shown bright promises in stable integration and long-term effectiveness when integrating with tissues, indicating a future trend in the design of biodevices.

In the way of developing wearable and implantable biodevices for seamless integration and high-efficiency interaction, undesirable bioadaptions between biodevices and tissues have become major challenges hindering the application perspectives. With recent advances in dynamic bio-interfaces onmulti-scales (molecular-, micro-/nano-, and macro-scales), biodevices with enhanced bio-adaptions have been designed and developed under the principles of biomimetics. Assisted by dynamic bio-interfaces, the biodevices can accommodate the mechanics and shapes of body tissues, finally achieving functional adaptions and behaving superior performances in the interaction and integration with human bodies. Though multi-scale bio-adaptions cannot be integrated into one biodevice yet, many recent research works have shown great potentials and enlightened the avenues of the field. It can be envisioned that the biodevices enabling multi-scale bioadaptions will be finally fulfilled through introducing more “intelligence” within the design of dynamic bio-interfaces, which will certainly rely on extensive innovations of new materials, control strategies, and integrating technologies. The perspectives of creating a superhero like the “Iron Man” that possesses capabilities far ahead of normal people may someday come true through equipping human beings with advanced brain-machine interfaces or artificial organs, along with the ever evolution of biodevices enabling reliable and seamless integration with human bodies.

Credit author statement

X. Du and Q. Zhao conceived the topic, prepared the draft and revised the manuscript.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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