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1	QIU C, WANG B, ZHANG N, et al. Transparent ferroelectric crystals with ultrahigh piezoelectricity[J]. Nature, 2020,577(7790): 350-354.	69.50	190
2	ZHANG P, GAO D, AN K, et al., A programmable polymer library that enables the construction of stimuli-responsive nanocarriers containing logic gates[J]. Nature Chemistry, 2020, 12(4), 381-390.	24.27	66
3	LIU H, ZhANG S, LI Z, et al., Harnessing the wide-range strain sensitivity of bilayered PEDOT: PSS films for wearable health monitoring[J]. Matter, 2021, 4(9), 2886-2901.	19.97	14
4	LI Z, ZHANG S, CHEN Y, et al. Gelatin Methacryloyl-Based Tactile Sensors for Medical Wearables[J]. Advanced Functional Materials, 2020,30(49): 2003601.	19.92	51
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Article

Transparent ferroelectric crystals with ultrahigh piezoelectricity

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Transparent piezoelectrics are highly desirable for numerous hybrid ultrasound–optical devices ranging from photoacoustic imaging transducers to transparent actuators for haptic applications[1–7]. However, it is challenging to achieve high piezoelectricity and perfect transparency simultaneously because most high-performance piezoelectrics are ferroelectrics that contain high-density light-scattering domain walls. Here, through a combination of phase-field simulations and experiments, we demonstrate a relatively simple method of using an alternating-current electric field to engineer the domain structures of originally opaque rhombohedral $Pb(Mg_{1/3}Nb_{2/3})O_3$-$PbTiO_3$ (PMN-PT) crystals to simultaneously generate near-perfect transparency, an ultrahigh piezoelectric coefficient d_{33} (greater than 2,100 picocoulombs per newton), an excellent electromechanical coupling factor k_{33} (about 94 per cent) and a large electro-optical coefficient γ_{33} (approximately 220 picometres per volt), which is far beyond the performance of the commonly used transparent ferroelectric crystal $LiNbO_3$. We find that increasing the domain size leads to a higher d_{33} value for the [001]-oriented rhombohedral PMN-PT crystals, challenging the conventional wisdom that decreasing the domain size always results in higher piezoelectricity[8–10]. This work presents a paradigm for achieving high transparency and piezoelectricity by ferroelectric domain engineering, and we expect the transparent ferroelectric crystals reported here to provide a route to a wide range of hybrid device applications, such as medical imaging, self-energy-harvesting touch screens and invisible robotic devices.

Achieving simultaneous high piezoelectricity and perfect transparency in a piezoelectric material has long been a challenge. For example, traditional high-performance piezoelectric transducers are typically made from perovskite ferroelectric ceramics and crystals with chemical compositions that are close to their morphotropic phase boundaries (MPBs), such as $Pb(Zr,Ti)O_3$ (PZT) ceramics and domain-engineered PMN-PT crystals. These materials possess very high d_{33} and k_{33} values[11–14], but they are usually opaque in the visible-light spectrum. On the other hand, the commonly used transparent piezoelectric $LiNbO_3$ crystals and polyvinylidine fluoride (PVDF) polymers[6,7] have good transparency but much lower d_{33} and k_{33} values ($LiNbO_3$: $d_{33} < 40$ pC N^{-1}, $k_{33} \approx 47\%$; PVDF: $d_{33} \approx 20$ pC N^{-1}, $k_{33} \approx 16\%$) that severely limit the acoustic source level, bandwidth and sensitivity of the transducers.

In addition to the extrinsic effects, such as porosity and grain boundaries, which are ubiquitous in ceramics, the poor transparency in PZT ceramics and domain-engineered PMN-PT crystals is closely associated with light scattering and reflection from their ferroelectric domain walls. There are two possible approaches to reducing the light-scattering domain walls. The first is to pole a ferroelectric crystal along the polar direction to achieve a single-domain state. However, the d_{33} value of such single-domain PMN-PT crystals is generally very low[13,14]—much lower than that of [001]-poled multidomain rhombohedral PMN-PT crystals (>1,500 pC N^{-1}). In principle, one could first pole a rhombohedral PMN-PT crystal along the [111] direction to achieve a single-domain state with good transparency, then rotate the crystal to the [001] direction to guarantee high longitudinal piezoelectricity. However, this approach is not feasible in practice (see Methods for a detailed explanation). The second approach is to dramatically reduce the domain sizes by breaking the domains into polar nanoregions with spatial sizes (a few to tens of nanometres) much smaller than the wavelength of visible light, thus greatly improving their light transparency—as observed in La-doped PZT[15,16]. However, improving the transparency using polar nanoregions is achieved at the expense of a markedly reduced remanent polarization and thus very low d_{33} values; therefore, despite more than 50 years of effort, optical functionalities in high-performance piezoelectrics have not been realized.

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A programmable polymer library that enables the construction of stimuli-responsive nanocarriers containing logic gates

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Stimuli-responsive biomaterials that contain logic gates hold great potential for detecting and responding to pathological markers as part of clinical therapies. However, a major barrier is the lack of a generalized system that can be used to easily assemble different ligand-responsive units to form programmable nanodevices for advanced biocomputation. Here we develop a programmable polymer library by including responsive units in building blocks with similar structure and reactivity. Using these polymers, we have developed a series of smart nanocarriers with hierarchical structures containing logic gates linked to self-immolative motifs. Designed with disease biomarkers as inputs, our logic devices showed site-specific release of multiple therapeutics (including kinase inhibitors, drugs and short interfering RNA) in vitro and in vivo. We expect that this 'plug and play' platform will be expanded towards smart biomaterial engineering for therapeutic delivery, precision medicine, tissue engineering and stem cell therapy.

Variations in physiological parameters, such as pH, redox balance, enzymes, metabolites, temperature and shear force, are important hallmarks for the genesis, development and prognosis of human diseases (for example, infection, cancer, heart disorders and neurodegeneration), presenting as promising diagnostic biomarkers and therapeutic targets[1–3]. Particularly in cancer, autologous dysregulation, as well as microenvironmental signals released by stromal cells (for example, matrix metalloproteinases, cytokines, chemokines and hypoxia), promotes tumour stemness and drives drug resistance, invasion and metastasis, accounting for the majority of clinical relapse and deaths[4–6]. To leverage the pathological cues for precise treatment, smart materials that undergo degradation or conformational change in response to external or endogenous stimuli have been engineered for targeted delivery and controlled drug release in lesion sites, showing significant improvement in enhancing treatment efficacy and reducing off-target effects[7,8]. However, to block metastatic signalling pathways, most combinatorial therapies require the coadministration and sequential release of multiple therapeutics, such as drugs, inhibitors, antibodies and gene strands, at the right time and place, which is a daunting challenge for single-stimulus responsive materials[9–11]. Another issue confronting researchers is that many physiological species dynamically change during disease progression and also exist in normal tissues, potentially hindering treatment that is exclusive only to the disease[4]. Thus, multiple responsive materials with programmed functions, especially logic-based biocomputation, are urgently needed to enhance controllability for activated targeting and site-specific release.

Biocomputation has the capability to sense, analyse and modulate chemical, mechanical or electronic signals in biological systems and follow a user-programmed Boolean logic-based algorithm to yield a functional output[12]. DNA and RNA are the most promising scaffolds with which to construct highly programmable logic devices that can be rationally designed at a molecular level and operate computations by strand displacement, enzyme cleavage and aptamer recognition with gene strands, metal ions, small molecules and receptors as inputs, thus making rapid progress in drug delivery, cellular imaging, genome editing and information storage[12–18]. Despite working well in test tubes, the effectiveness and reliability of most nucleic acid-based devices in biological systems are in some doubt because these highly charged macromolecules suffer from serious degradation, clearance, immune recognition and delivery issues[17]. Biocomputation can also use protein/peptide-based logic systems, but such systems have the same stability and delivery problems, as well as limited inputs (usually enzymes) and complex structures (rigid folding), making complicated computational operations a distinct challenge[15,19]. By contrast, responsive polymers represent synthetic smart materials that can respond to a wide range of pathological cues, providing a powerful tool for diagnostics, drug delivery and tissue engineering[20–23]. However, owing to their highly diverse chemistry and structural complexity, most multi-stimuli-responsive polymer-based particles, films and hydrogels have been developed

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Harnessing the Wide-range Strain Sensitivity of Bilayered PEDOT:PSS Films for Wearable Health Monitoring

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Declaration of Interests

The authros declare no competing interests.

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Gelatin Methacryloyl-Based Tactile Sensors for Medical Wearables

Zhikang Li, Shiming Zhang, Yihang Chen, Haonan Ling, Libo Zhao,* Guoxi Luo, Xiaochen Wang, Martin C. Hartel, Hao Liu, Yumeng Xue, Reihaneh Haghniaz, KangJu Lee, Wujin Sun, HanJun Kim, Junmin Lee, Yichao Zhao, Yepin Zhao, Sam Emaminejad, Samad Ahadian, Nureddin Ashammakhi, Mehmet R. Dokmeci, Zhuangde Jiang, and Ali Khademhosseini**

Gelatin methacryloyl (GelMA) is a widely used hydrogel with skin-derived gelatin acting as the main constituent. However, GelMA has not been used in the development of wearable biosensors, which are emerging devices that enable personalized healthcare monitoring. This work highlights the potential of GelMA for wearable biosensing applications by demonstrating a fully solution-processable and transparent capacitive tactile sensor with microstructured GelMA as the core dielectric layer. A robust chemical bonding and a reliable encapsulation approach are introduced to overcome detachment and water-evaporation issues in hydrogel biosensors. The resultant GelMA tactile sensor shows a high-pressure sensitivity of 0.19 kPa^{-1} and one order of magnitude lower limit of detection (0.1 Pa) compared to previous hydrogel pressure sensors owing to its excellent mechanical and electrical properties (dielectric constant). Furthermore, it shows durability up to 3000 test cycles because of tough chemical bonding, and long-term stability of 3 days due to the inclusion of an encapsulation layer, which prevents water evaporation (80% water content). Successful monitoring of various human physiological and motion signals demonstrates the potential of these GelMA tactile sensors for wearable biosensing applications.

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RESEARCH ARTICLE

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Cascade-Amplifying Synergistic Therapy for Intracranial Glioma via Endogenous Reactive Oxygen Species-Triggered "All-in-One" Nanoplatform

Pengying Wu, Mingting Zhu, Yan Li, Zhen Ya, Yabo Yang, Yuchen Yuan, Wei Dong, Shifang Guo, Shukuan Lu, Lei Zhang, Yujin Zong, and Mingxi Wan**

Targeted delivery of drug-loaded nanoparticles to brain tumors is exceptionally difficult due to the blood-brain barrier (BBB). In addition, several chemotherapeutic drugs induce autophagy, which protects the cells from apoptosis and mitigates the therapeutic effect. A novel "all-in-one" nanoparticles (AMPTL) consisting of endogenous reactive oxygen species-cleavable thioketal linkers conjugated to paclitaxel (PTX) and autophagy inhibitor 3-methyladenine, and angiopep-2 peptide-modified DSPE-PEG_{2K} is developed. AMPTL inhibits autophagy in the C6 glioma cells, as indicated by fewer autophagic vesicles, lower LC3-II expression and accumulation of SQSTM1/P62, and significantly upregulates p53 and the pro-apoptotic Bax and cleaved caspase-3 proteins. In addition, AMPTL treatment induces cell cycle arrest at the G2/M phase. Thus, inhibition of autophagy in the AMPTL-treated glioma cells sensitizes them to PTX-induced cell cycle arrest and apoptosis. Furthermore, focused pulse ultrasound and microbubbles enhances the delivery of AMPTL to intracranial glioma tissues by reversibly opening the BBB, which significantly inhibits xenograft growth and markedly improves survival rates of the tumor-bearing mice. Taken together, combining non-invasive BBB opening with autophagy inhibitors and chemotherapeutic drugs can achieve cascade-amplifying synergistic therapeutic effects against glioma.

1. Introduction

Efficient delivery of therapeutic agents across the blood-brain barrier (BBB) is a major challenge in the treatment of brain diseases. BBB, a specialized cerebro-vascular system consisting of brain endothelial cells, blocks 98% of the drug molecules (>400 Da) from entering the brain.[1] Glioma is the most common and aggressive subtype of primary central nervous system brain tumor, and is associated with high morbidity and mortality. Since glioma cells leave the BBB relatively intact and invade the surrounding healthy tissues,[2] it is largely recalcitrant to chemotherapy. Surgical resection is the first-line treatment for glioma, although its therapeutic potential is limited due to the invasive and aggressive nature of glioma cells.[3] The mean overall survival of glioma patients after surgical resection is only 15 months.[4] In addition, autophagy can also desensitize glioma cells to surgery, chemotherapy and radiotherapy, which further worsens patient prognosis.[5] Despite significant advances in our understanding of the molecular mechanisms underlying glioma progression, novel and effective therapeutic targets need to be identified.

Non-invasive focused ultrasound (US) has shown encouraging results in the detection and treatment of brain disorders such as Alzheimer's disease, Parkinson's disease, and glioma.[6] US increases vascular permeability in the presence of intravascular microbubbles (MBs), which facilitates targeted delivery and accumulation of drugs into brain tissue.[7] Compared to conventional cerebral blood barrier blocking methods like intracranial local injection and systemic hypertonic solution injection, ultrasonic radiation has the advantages of deep penetration, non-invasiveness, low cost, safety and high reproducibility, and allows drug delivery across the skin and BBB.[8] Clinical trials are currently underway on the efficacy of US and MBs for opening BBB as a treatment strategy against Alzheimer's disease and glioma.[9] Preclinical studies have established that BBB opening with US pulses and MBs can enhance the delivery of antibodies, chemotherapeutic drugs and nanoparticles to normal and diseased brain tissues.[4,6c]

Autophagy is a conserved self-digestion process that occurs in response to stress and clears non-essential organelles or misfolded proteins to ensure cell survival.[10] Studies increasingly show that autophagy is an important factor in cancer progression and chemoresistance.[11] Autophagy provides energy for the rapidly proliferating cancer cells, and allows them to survive in the inhospitable tumor microenvironment.[12] Furthermore, pharmacological inhibition of autophagy or silencing of autophagy-related genes can sensitize cancer cells to multiple

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Human-on-Leaf-Chip: A Biomimetic Vascular System Integrated with Chamber-Specific Organs

Mao Mao, Ho Pan Bei, Chun Hei Lam, Pengyu Chen, Shuqi Wang, Ying Chen, Jiankang He, and Xin Zhao**

The vascular network is a central component of the organ-on-a-chip system to build a 3D physiological microenvironment with controlled physical and biochemical variables. Inspired by ubiquitous biological systems such as leaf venation and circulatory systems, a fabrication strategy is devised to develop a biomimetic vascular system integrated with freely designed chambers, which function as niches for chamber-specific vascularized organs. As a proof of concept, a human-on-leaf-chip system with biomimetic multiscale vasculature systems connecting the self-assembled 3D vasculatures in chambers is fabricated, mimicking the in vivo complex architectures of the human cardiovascular system connecting vascularized organs. Besides, two types of vascularized organs are built independently within the two halves of the system to verify its feasibility for conducting comparative experiments for organ-specific metastasis studies in a single chip. Successful culturing of human hepatoma G2 cells (HepG2s) and mesenchymal stem cells (MSCs) with human umbilical vein endothelial cells (HUVECs) shows good vasculature formation, and organ-specific metastasis is simulated through perfusion of pancreatic cancer cells and shows distinct cancer encapsulation by MSCs, which is absent in HepG2s. Given good culture efficacy, study design flexibility, and ease of modification, these results show that the bioinspired human-on-leaf-chip possesses great potential in comparative and metastasis studies while retaining organ-to-organ crosstalk.

Noteworthy efforts have been devoted to creating organ-on-a-chip system for culturing living cells in perfused, miniaturized platform, in order to satisfy the urgent needs of establishing physiologically functional tissues or organs as in vitro disease models for drug screening and disease pathology studies.[1–3] To remedy the limitations of conventional 2D or 3D culture systems such as lack of supportive vasculature formation and inability to accommodate biomimetic dynamic cultures, organ-on-chips are expected to recapitulate the in vivo 3D tissue multiscale architecture and the complex organ-specific biophysical and biochemical microenvironments.[4,5] Vasculature is essential for interconnection between organs and serves as a semipermeable barrier to dynamically regulate the exchange of molecules and cells between the flowing fluids and surrounding tissue, closely related to some critical diseases such as metastasis and inflammatory diseases.[6–8]

Numerous approaches have been developed over the past decades to incorporate

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CELL BIOLOGY

Nanoscale integrin cluster dynamics controls cellular mechanosensing via FAKY397 phosphorylation

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Transduction of extracellular matrix mechanics affects cell migration, proliferation, and differentiation. While this mechanotransduction is known to depend on the regulation of focal adhesion kinase phosphorylation on Y397 (FAKpY397), the mechanism remains elusive. To address this, we developed a mathematical model to test the hypothesis that FAKpY397-based mechanosensing arises from the dynamics of nanoscale integrin clustering, stiffness-dependent disassembly of integrin clusters, and FAKY397 phosphorylation within integrin clusters. Modeling results predicted that integrin clustering dynamics governs how cells convert substrate stiffness to FAKpY397, and hence governs how different cell types transduce mechanical signals. Existing experiments on MDCK cells and HT1080 cells, as well as our new experiments on 3T3 fibroblasts, confirmed our predictions and supported our model. Our results suggest a new pathway by which integrin clusters enable cells to calibrate responses to their mechanical microenvironment.

INTRODUCTION

The ways that cells transduce and respond to their mechanical microenvironments underlie pathological remodeling in metastasis and fibrosis, and physiological remodeling in development and stem cell differentiation (*1*–*3*). A variety of potential mechanosensors are available to cells including various adhesion proteins such as integrin, focal adhesion kinase (FAK), talin, and vinculin (*4*). In many cells, a relatively high substrate stiffness up-regulates phosphorylation of FAK on Y397 (FAKpY397) (Fig. 1A), which affects cell behaviors including proliferation, migration, and differentiation (*5*). However, the molecular mechanism by which cell adhesions enable this stiffness sensing via FAKpY397 remains elusive.

A hypothesis proposed recently is that the dynamics of nanoscale integrin clusters within focal adhesions (FAs) governs mechanosensing via FAKpY397 (*6*). The loose aggregates containing tight clusters of integrins with a size of ~100 nm and composed of ~20 to 50 integrin molecules (Fig. 1B), as identified by super-resolution imaging (*7*), are believed to be sites for FAKY397 phosphorylation. Substrate stiffness–dependent cluster dynamics affects the ability of integrin molecules to form adhesions (*8*) and is hypothesized to play a key role in cellular decisions about the suitability of a microenvironment for growth and differentiation. Integrin clusters turn over through clustering-disassembly dynamics on the time scale of minutes (*9*), but their lifetimes can be prolonged by the traction of actomyosin-based sarcomere-like contractile units (CUs) (*10*). These dynamics may be related to the phosphorylation of FAKY397 (Fig. 1C).

On the basis of these observations, we hypothesized that integrin clusters serve as platforms for substrate stiffness–dependent FAKY397 activation. To test our hypothesis, we developed a mathematical model integrating submodels of (i) integrin clustering, (ii) stiffness-dependent integrin cluster disassembly, and (iii) FAKY397 phosphorylation within integrin clusters. With this model, we assessed several biomechanical and biochemical processes that appear to play important roles in integrin clustering and clustered integrin–mediated FAKY397 phosphorylation.

RESULTS

Spatial Monte Carlo model of integrin clustering kinetics

To test our hypothesis, we developed a coarse-grained spatial Monte Carlo model of integrin clustering. Integrin clustering requires activation of integrin molecules to their high ligand binding affinity state by the talin head domain (*11*, *12*), with activation and inactivation rate constants of k_{a+} and k_{a-}, respectively (Fig. 1D). Activated integrins could bind to ligand with a rate of k_{b+} and unbind upon separating from clusters with a rate of k_{b-} (Fig. 1D). Integrin molecules aggregate or separate from neighbors by binding or unbinding via (i) membrane-bound PI(4,5)P_2 (phosphatidylinositol 4,5-bisphosphate) molecules (*12*) and (ii) integrin transmembrane domains (ITDs) (*13*) with binding and unbinding rates of k_{c+} and k_{c-}, respectively (Fig. 1E). Beginning with a random distribution of integrin molecules on the membrane lattice, the number of clustered integrins increases with computational time (Fig. 1F).

To quantify these dynamics, we computed the average number of integrin molecules per cluster ("integrin cluster size," N_a) and the spatial density of integrin clusters ("integrin cluster number," M_a) after reaching a steady state (Fig. 1E). The distribution of N_a fits a power function well (red line in Fig. 1G)

$$P = \alpha x^{\beta} \quad (1)$$

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Directed cell migration towards softer environments

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How cells sense tissue stiffness to guide cell migration is a fundamental question in development, fibrosis and cancer. Although durotaxis—cell migration towards increasing substrate stiffness—is well established, it remains unknown whether individual cells can migrate towards softer environments. Here, using microfabricated stiffness gradients, we describe the directed migration of U-251MG glioma cells towards less stiff regions. This 'negative durotaxis' does not coincide with changes in canonical mechanosensitive signalling or actomyosin contractility. Instead, as predicted by the motor–clutch-based model, migration occurs towards areas of 'optimal stiffness', where cells can generate maximal traction. In agreement with this model, negative durotaxis is selectively disrupted and even reversed by the partial inhibition of actomyosin contractility. Conversely, positive durotaxis can be switched to negative by lowering the optimal stiffness by the downregulation of talin—a key clutch component. Our results identify the molecular mechanism driving context-dependent positive or negative durotaxis, determined by a cell's contractile and adhesive machinery.

The capacity of living cells to undergo controlled migration is critical for tissue homeostasis and development, and underlies pathological conditions like cancer metastasis[1,2]. Cells migrate in response to chemical and physical cues including the elasticity, or stiffness, of the surrounding extracellular matrix (ECM). The well-known tendency for many cells to migrate towards stiffer substrates, known as durotaxis[3–8], has implications for both developmental morphogenesis[9,10] and cancer cell invasion[8,11,12].

Despite progress in empirically identifying environmental conditions and molecular components that enable or promote durotaxis[3,5,13–15], our understanding of its fundamental mechanisms in different cell types is lacking. A long-standing mathematical model for cell migration is based on the motor–clutch mechanism[16–19], in which F-actin filaments polymerize against the plasma membrane to push the cell edge forward while being simultaneously pulled away from the cell edge by adenosine triphosphate (ATP)-dependent myosin II ('molecular motors') and pushed by force from the ATP-dependent polymerization itself. Retrograde F-actin flow can be mitigated by mechanical connections or 'clutches', typically integrin-mediated adhesions, between the F-actin and ECM to generate traction and bias cell movement towards more adhesive environments[20,21]. These traction forces are critical for cell migration; as a result, they have also been linked to durotaxis. For example, fibroblasts on stiffness gradients exhibit asymmetric traction that has been postulated to directly contribute to their polarization and migration up the gradient[5,22]. Recently, differences in intracellular contractility and adhesivity to the ECM have been proposed to explain why some cells are more prone to durotax than others[12]. Interactions between actomyosin machinery and integrin-mediated adhesions have also been implicated in neuronal growth and mechanosensitive pathfinding[23–25]. However, the unifying principles underlying these behaviours across cell types have not been established.

Recently, cellular traction forces were shown to be maximal on substrates of an 'optimal stiffness' that can be predicted by the motor–clutch model[18,19,26–30]. However, the biological relevance of this on cell behaviour remains to be fully elucidated. Due to the key role of traction in driving mesenchymal cell migration, we predicted that any cell whose adhesion dynamics are governed by the motor–clutch model could potentially migrate towards softer environments, if such environments were closer to the cell's optimal stiffness for maximal traction generation. We call this behaviour 'negative durotaxis'.

U-251MG glioblastoma cells undergo negative durotaxis

To test our hypothesis, we seeded U-251MG human glioblastoma cells, previously shown to exhibit maximal traction at an optimal stiffness of 5–10 kPa (Fig. 1a)[29], on fibronectin-functionalized polyacrylamide hydrogels having a continuous stiffness gradient of approximately 0.5–22.0 kPa (Supplementary Fig. 1a,b)[31]—a range

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Ex Vivo and *In Vivo* Monitoring and Characterization of Thermal Lesions by High-Intensity Focused Ultrasound and Microwave Ablation Using Ultrasonic Nakagami Imaging

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***Abstract*— The feasibility of ultrasonic Nakagami imaging to evaluate thermal lesions by high-intensity focused ultrasound and microwave ablation was explored in *ex vivo* and *in vivo* liver models. Dynamic changes of the ultrasonic Nakagami parameter in thermal lesions were calculated, and ultrasonic B-mode and Nakagami images were reconstructed simultaneously. The contrast-to-noise ratio (CNR) between thermal lesions and normal tissue was used to estimate the contrast resolution of the monitoring images. After thermal ablation, a bright hyper-echoic region appeared in the ultrasonic B-mode and Nakagami images, identifying the thermal lesion. During thermal ablation, mean values of Nakagami parameter showed an increasing trend from 0.72 to 1.01 for the *ex vivo* model and 0.54 to 0.72 for the *in vivo* model. After thermal ablation, mean CNR values of the ultrasonic Nakagami images were 1.29 dB (*ex vivo*) and 0.80 dB (*in vivo*), significantly higher ($p < 0.05$) than those for B-mode images. Thermal lesion size, assessed using ultrasonic Nakagami images, shows a good correlation to those obtained from the gross-pathology images (for the *ex vivo* model: length, $r = 0.96$; width, $r = 0.90$; for the *in vivo* model: length, $r = 0.95$; width, $r = 0.85$). This preliminary study suggests that ultrasonic Nakagami parameter may have a potential use in evaluating the formation of thermal lesions with better image contrast. Moreover, ultrasonic Nakagami imaging combined with B-mode imaging may be utilized as an alternative modality in developing monitoring systems for image-guided thermal ablation treatments.**

***Index Terms*— High-intensity focused ultrasound, microwave ablation, ultrasound imaging, Nakagami parameter, thermal ablation, monitoring.**

I. Introduction

IMAGE-GUIDED thermal ablation technologies, such as radiofrequency, microwave, laser, cryotherapy, and high-intensity focused ultrasound (HIFU), are emerging as precise methods of selectively and locally inducing irreversible cell injury, and ultimately assisting in tumor apoptosis and coagulative necrosis inside the body [1]–[5]. HIFU is a rapidly emerging non-invasive technique used to selectively and locally treat tumors located in various tissues, including the prostate [6], liver [7], kidney [8], uterine fibroids [9], brain [10], and breast [11], and more recently to treat neurological disorders [12]. Microwave ablation is a promising minimally invasive local therapeutic modality that destroys tumors by means of thermal coagulation or protein denaturation [13]. At present, MWA has been extensively used in the treatment of cancer in the liver, kidney, lung, breast, adrenal gland, bone, adenomyosis, and uterin fibroid [3], [13]. Potential clinic application of thermal ablation for treating various tissue cancers is now experiencing progress by taking advantage of recent advances in medical imaging techniques, such as magnetic resonance imaging (MRI) [14] and ultrasound (US) imaging for targeting and monitoring thermal ablation treatments [9], [10], [15].

Tissue necrosis induced by a focused ultrasound beam can be detected with MRI and the temperature sensitivity of proton resonance frequency (PRF) or relaxation time T_1 is then used to monitor temperature distribution [14], [16]. Magnetic resonance-guided focused ultrasound (MRgFUS)

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Electrohydrodynamic printing: a potential tool for high-resolution hydrogel/cell patterning

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ABSTRACT

Electrohydrodynamic printing has gained increasing attentions to fabricate micro/nanoscale patterns in a controlled and cost-effective manner. However, most of the existing studies focus on printing tiny dried fibres, which limits its applications in high-resolution cell printing. Here we investigated the feasibility of using electrohydrodynamic printing to pattern microscale liquid filaments. Process parameters like stage moving speed and substrate resistance were optimised to stably print polyvinyl alcohol (PVA) liquid lines with the smallest line width of 37.4 μm. Complex patterns like XJTU logo with constant or variable line width were successfully printed by dynamically adjusting the moving speed. Fluorescent microparticles, with a similar diameter to living cells, were patterned in a one-by-one manner along with the PVA filaments. It is envisioned that the presented electrohydrodynamic printing method could be potentially used to high-resolution hydrogel/cell patterning for the studies of microscale cell–cell interactions or organ printing.

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1. Introduction

Electrohydrodynamic printing, also known as electrohydrodynamic jetting or direct-writing, has recently attracted extensive attentions to fabricate micro/nanoscale patterns in a cost-effective manner (Huang *et al.* 2013, Onses et al. 2015). The principle of electrohydrodynamic printing is based on conventional electrospinning which employs high-voltage electric field to induce the ejecting of polymer filament, which is deposited into a user-specific pattern by controlling the substrate movement. Previous studies in electrohydrodynamic printing mainly focused on the effect of process parameters like needle-to-collector distance, high voltage, moving speed on the morphology and width of the printed single lines or fibres (Byun and Nguyen 2009). With the optimal parameters, electrohydrodynamic printing technique has been successfully used to fabricate microscale electronic, photonic and plasmonic devices (He *et al.* 2014, Onses *et al.* 2015).

The application of electrohydrodynamic printing into biomedical fields enables to generate biomimetic micro/nanofibrous structures with the similar length scale to native collagen fibres (Kim *et al.* 2007). For example, melt-based electrohydrodynamic printing was developed to directly fabricate three-dimensional (3D) polycaprolactone scaffolds with the smallest filament diameter of 817 nm, which was found to direct cellular growth and promote the mechanical strength of chondrocyte–hydrogel constructs (Brown *et al.* 2011, Hochleitner *et al.* 2015, Visser *et al.* 2015). Solution-based electrohydrodynamic printing was also investigated to deposit microscale patterns from synthetic and natural biomaterials like collagen, polyethylene oxide and silk fibroin (Bayram *et al.* 2013, He *et al.* 2016). However, these investigations pursued to achieve high-resolution printing of dried fibres. Few studies so far have been conducted to verify the feasibility of printing microscale liquid filaments, which is critical to translate electrohydrodynamic printing into a high-resolution single cell printing technique.

Recent studies in cell electrospinning have demonstrated that living cells could maintain relatively high viability during the high-voltage ejecting process (Zanatta *et al.* 2012, Sampson *et al.* 2013). Gasperini *et al.* (2015) further employed electrospinning-based printer to deposit alginate hydrogel containing living cells. However, these attempts were mainly limited to randomly distribution of cells or large filament size. It is technically difficult to realise microscale hydrogel or single cell patterning, which is also the main challenge of conventional 3D bioprinting techniques (Bhuthalingam *et al.* 2015, Koudan *et al.* 2016, Tse *et al.* 2016). Here we investigated the feasibility of using electrohydrodynamic printing to fabricate microscale liquid filaments as well as pattern single microparticles. Polyvinyl alcohol (PVA)

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Short communication

The effect of interface microstructure on interfacial shear strength for osteochondral scaffolds based on biomimetic design and 3D printing

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ABSTRACT

Interface integration between chondral phase and osseous phase is crucial in engineered osteochondral scaffolds. However, the integration was poorly understood and commonly failed to meet the need of osteochondral scaffolds. In this paper, a biphasic polyethylene glycol (PEG)/β-tricalcium phosphate (β-TCP) scaffold with enhanced interfacial integration was developed. The chondral phase was a PEG hydrogel. The osseous phase was a β-TCP ceramic scaffold. The PEG hydrogel was directly cured on the ceramic interface layer by layer to fabricate osteochondral scaffolds by 3D printing technology. Meanwhile, a series of interface structure were designed with different interface pore area percentages (0/10/20/30/40/50/60%), and interfacial shear test was applied for interface structure optimization (n = 6 samples/group). The interfacial shear strength of 30% pore area group was nearly three folds improved compared with that of 0% pore area percentage group, and more than fifty folds improved compared with that of traditional integration (5.91 0.59 kPa). In conclusion, the biomimetic PEG/β-TCP scaffolds with interface structure enhanced integration show promising potential application for osteochondral tissue engineering.

1. Introduction

Delamination of engineered cartilage jeopardizes the outcome of cartilage repair [1]. Interface integration between chondral phase and osseous phase is crucial in engineered osteochondral scaffold [2,3]. However, the integration of biphasic osteochondral scaffolds reported to date was mainly enhanced by suturing [2], gluing [4,5] or crosslinking [6] and the integration failed to meet the need of osteochondral scaffolds. Recently, incorporation of calcium phosphate compounds such as CPP (calcium polyphosphate) [7], HA (hydroxyapatite) [8] or β-GP (β-glycerophosphate) [9] was reported to promote the interface strength *via* biological bonding [10] over time, the interface shear strength was still two or three orders of magnitude less than the native tissue [3,9].

The natural osteochondral integration was enhanced by osteochondral interface [3]. The subchondral bone was anchored tightly with cartilage in "comb-anchor" [11] or interdigitations to reduce stress concentrations [12], our previous study also confirmed the presence of gomphosis and hole like structure on native subchondral bone plate [13,14]. However, interface structure was seldom considered in available biphasic osteochondral study.

Stereolithograhy (SL) is an accurate and easy-to-use 3D printing technology to fabricate complex structures individually in a manner of layer by layer [15]. Poly(ethylene glycol) (PEG) hydrogels have been applied extensively for *in vitro* and *in vivo* cartilage tissue engineering [16–18]. Our previous study showed that PEG hydrogel with desired mechanical property could be prepared *via* controlling the concentration of PEGDA (PEG diacrylate) solution and stereolithograhy parameters [19], thus it is feasible to integrate the PEG cartilage phase directly with underlying osseous part using 3D printing technology.

In the present study, we developed a new PEG/β-TCP osteochondral scaffold integrated *via* biomimetic interface structure design and 3D printing technology. The interfacial shear test was carried out to determine which structure could be efficient to enhance interfacial integration. We believed that the interface enhanced hydrogel-ceramic osteochondral scaffolds could provide stable environments for osteochondral regeneration.

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Design and fabrication of biomimetic multiphased scaffolds for ligament-to-bone fixation

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ABSTRACT

Conventional ligament grafts with single material composition cannot effectively integrate with the host bones due to mismatched properties and eventually affect their long-term function *in vivo*. Here we presented a multi-material strategy to design and fabricate composite scaffolds including ligament, interface and bone multiphased regions. The interface region consists of triphasic layers with varying material composition and porous structure to mimic native ligament-to-bone interface while the bone region contains polycaprolactone (PCL) anchor and microchanneled ceramic scaffolds to potentially provide combined mechanical and biological implant-bone fixation. Finite element analysis (FEA) demonstrated that the multiphased scaffolds with interference value smaller than 0.5 mm could avoid the fracture of ceramic scaffold during the implantation process, which was validated by *in-vitro* implanting the multiphased scaffolds into porcine joint bones. Pull-out experiment showed that the initial fixation between the multiphased scaffolds with 0.47 mm interference and the host bones could withstand the maximum force of 360.31 97.51 N, which can be improved by reinforcing the ceramic scaffolds with biopolymers. It is envisioned that the multiphased scaffold could potentially induce the regeneration of a new bone as well as interfacial tissue with the gradual degradation of the scaffold and subsequently realize long-term biological fixation of the implant with the host bone.

1. Introduction

In vivo, anterior cruciate ligament (ACL) strongly integrates with bone tissue through a transition fibrocartilage interface, which plays an important role in minimizing stress concentrations during load transmission between the dissimilar tissues of ligament and bone [1,2]. As one of the most frequently injured ligaments, ACL has very limited self-healing potential. Ligament grafts were commonly used to restore the biological functions of injured ACL. For most of the existing ligament grafts, they were clinically inserted into bone tunnels and mechanically fixed with the host bones using interference screws. The mismatch between soft ligament grafts and hard bone tissues in mechanical and biological properties has been found to induce the formation of scar tissues and eventually hinder the osteointegration of implanted ligament grafts, which has been considered as one of the crucial issues for graft failure [3]. Although several strategies have been developed to promote osteointegration by incorporating osteoinductive factors (*e.g.*, bone morphogenetic protein, hydroxyapatite) or altering structural organizations at the graft insertion site [4–7], long-term stability of graft-bone fixation might depend on the regeneration of multiple tissue interface.

Interfacial tissue engineering has shown great promise in regenerating ligament/bone interface by using graded or multiphased scaffolds either with distinct material compositions or seeded with multiple cell types [8–11]. Spalazzi et al. [12,13] developed a triphasic scaffold that contained soft ligament region, intermediate fibrocartilage region and hard bone region to mimic native ligament insertion. The triphasic scaffolds pre-seeded with multiple cell types of osteoblast, chondrocytes and fibroblast were found to support zonal cellular distribution, facilitate phase-specific matrix deposition and finally enable multi-tissue regeneration *in vitro* and *in vivo*. Electrospun nanofibrous scaffolds with material or/and structure gradients were also investigated to facilitate interface regeneration [14–17]. Although some promising progress has been achieved in these preliminary attempts, few strategies have been reported so far to effectively incorporate these multiphased scaffolds into ligament grafts and simultaneously consider their initial fixation with the host bones.

Here we sought to fabricate a multiphased ligament/bone composite scaffold mainly including biodegradable polycaprolactone (PCL) anchor, microfluidic bone tissue-engineered scaffold, microfibrous ligament graft and biomimetic interface, which could provide initial mechanical implant-bone fixation and potentially facilitate new bone ingrowths

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Viewpoint

Xi'an consensus on magnetic surgery

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The interest in magnetic surgery has increased over the past decade following the development of minimally invasive procedures.

Magnetic surgery is defined as surgical treatment by utilization of magnetic technology.

Specifically, magnetic surgery includes but is not limited to magnetic compression anastomosis (Magnamosis), magnetic anchoring technique, magnetic navigation technique, magnetic sphincter augmentation, self-assembling magnets for endoscopic intestinal bypass, magnetic compression ostomy, correction of congenital deformities, etc. Magnetic surgery is developing rapidly and created a new surgical field.

The advantages of magnetic compression anastomosis include:

(I) Non-penetrating compression anastomosis, minimizing inflammatory reaction;
(II) Incision-less and suture-less anastomosis;
(III) Easily applied to minimally-invasion procedures;
(IV) Self-assembling for creation of anastomosis;
(V) Self-adjusting according to individual tissue thickness.

The disadvantages of magnetic compression anastomosis include:

(I) MRI inspection is limited;
(II) Application may be limited patients with pacemakers;
(III) Magnetic force is difficult to be precisely controlled;
(IV) Possible side effects of long-term exposure to magnetic field (as yet unknown).

The principle of Magnamosis of hollow viscus is based on the natural process of tissue remodeling and healing. A constant pressure is exerted on the apposed walls of two visceral segments by magnetic devices leading to transmural ischemia, necrosis, and healing with, finally,

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Biological network extraction from scientific literature: state of the art and challenges

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Abstract

Networks of molecular interactions explain complex biological processes, and all known information on molecular events is contained in a number of public repositories including the scientific literature. Metabolic and signalling pathways are often viewed separately, even though both types are composed of interactions involving proteins and other chemical entities.

It is necessary to be able to combine data from all available resources to judge the functionality, complexity and completeness of any given network overall, but especially the full integration of relevant information from the scientific literature is still an ongoing and complex task.

Currently, the text-mining research community is steadily moving towards processing the full body of the scientific literature by making use of rich linguistic features such as full text parsing, to extract biological interactions. The next step will be to combine these with information from scientific databases to support hypothesis generation for the discovery of new knowledge and the extension of biological networks.

The generation of comprehensive networks requires technologies such as entity grounding, coordination resolution and co-reference resolution, which are not fully solved and are required to further improve the quality of results. Here, we analyse the state of the art for the extraction of network information from the scientific literature and the evaluation of extraction methods against reference corpora, discuss challenges involved and identify directions for future research.

Keywords: *text mining; network extraction; event extraction*

INTRODUCTION

A biological network is represented in a graph structure composed of nodes that denote biomolecules and edges between the nodes representing the interactions or reactions between the biomolecules. Network representations serve many purposes in bioinformatics, and most importantly, networks are used to judge the functional behaviour of interaction networks on the molecular level. Network representations are used to simulate, analyse and visualize the responses of protein interaction networks, metabolic pathways, specific synapses and even whole systems such as an organ, e.g. the liver or the brain. Studying the topological structure and the functional responses of such systems aims to reveal yet undiscovered mechanisms that could explain or improve specific

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Review Paper

Overview of the detection methods for equilibrium dissociation constant K_D of drug-receptor interaction

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ABSTRACT

Drug-receptor interaction plays an important role in a series of biological effects, such as cell proliferation, immune response, tumor metastasis, and drug delivery. Therefore, the research on drug-receptor interaction is growing rapidly. The equilibrium dissociation constant (K_D) is the basic parameter to evaluate the binding property of the drug-receptor. Thus, a variety of analytical methods have been established to determine the K_D values, including radioligand binding assay, surface plasmon resonance method, fluorescence energy resonance transfer method, affinity chromatography, and isothermal titration calorimetry. With the invention and innovation of new technology and analysis method, there is a deep exploration and comprehension about drug-receptor interaction. This review discusses the different methods of determining the K_D values, and analyzes the applicability and the characteristic of each analytical method. Conclusively, the aim is to provide the guidance for researchers to utilize the most appropriate analytical tool to determine the K_D values.

Contents

1. Introduction

The type of drug target is divided into receptor, enzyme, nucleic acid, and so on. There are about 40% drugs which interact with the corresponding receptors in order to exert their pharmacological effects. When the ligands (first messenger) combine with the corresponding receptor, a signal cascade reaction occurs through the second messenger in the cell, resulting in a series of biological effects, such as immune response and cell proliferation [1–3]. Therefore, it is very necessary to study the interaction between drugs and receptors, which contributes to understanding the mechanisms of drugs [4–8]. The equilibrium dissociation constant (K_D) is the basic parameter to evaluate the binding properties of the drug-receptor [9–11]. Thus, it is of great importance to determine the K_D values of the drugs.

A variety of analytical methods have been established to determine the K_D values since the 1960s, including radioligand binding assay (RBA) [12], surface plasmon resonance (SPR) [13], fluorescence energy resonance transfer method (FRET) [14], affinity chromatography [15], and isothermal titration calorimetry (ITC) [16].

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Unsupervised MR-to-CT Synthesis Using Structure-Constrained CycleGAN

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***Abstract*— Synthesizing a CT image from an available MR image has recently emerged as a key goal in radiotherapy treatment planning for cancer patients. CycleGANs have achieved promising results on unsupervised MR-to-CT image synthesis; however, because they have no direct constraints between input and synthetic images, cycleGANs do not guarantee structural consistency between these two images. This means that anatomical geometry can be shifted in the synthetic CT images, clearly a highly undesirable outcome in the given application. In this paper, we propose a structure-constrained cycleGAN for unsupervised MR-to-CT synthesis by defining an extra structure-consistency loss based on the modality independent neighborhood descriptor. We also utilize a spectral normalization technique to stabilize the training process and a self-attention module to model the long-range spatial dependencies in the synthetic images. Results on unpaired brain and abdomen MR-to-CT image synthesis show that our method produces better synthetic CT images in both accuracy and visual quality as compared to other unsupervised synthesis methods. We also show that an approximate affine pre-registration for unpaired training data can improve synthesis results.**

***Index Terms*— MR-to-CT synthesis, CycleGAN, deep learning, MIND.**

I. Introduction

BOTH magnetic resonance (MR) and computed tomography (CT) images are essential and widely utilized in radiotherapy treatment planning (RTP) [1], [2]. For structural imaging with excellent soft-tissue contrast, MR imaging is good at precisely and reliably locating tumours and organs. However, MR images do not directly provide electron density information, which is indispensable in RTP for cancer patients. Although CT images provide electron density information, they lack good soft-tissue contrast. The acquisition of both CT and MR images of the patient is therefore usually part of the clinical workflow [3]. But acquisition of both images is time-consuming, costly, and requires accurate MR/CT registrations for optimal utility of the pair. If acquisition of the CT scan could be omitted in RTP, it would avoid these difficulties and also prevent the potential harmful effects of radiation exposure [4].

A variety of approaches have been proposed to synthesize a CT image from an MR image using *paired* MR and CT atlases, i.e., the pre-acquired pairs of non-rigidly aligned MR and CT volumes from the same patients [5]–[14]. For example, Nie *et al.* [12] trained a 3D fully convolutional network (FCN) using an adversarial learning strategy and then iteratively refined the synthetic CT results via an auto-context model. Although these methods can produce good synthetic images, they rely on a large number of paired CT and MR images, which are hard to obtain in practice, especially for specific MR tissue contrasts. To relax the requirement of paired training data, Wolterink *et al.* [15] proposed the use of a cycleGAN [16] for unpaired MR-to-CT synthesis. This approach uses a convolutional neural network (CNN) to learn the MR-to-CT mapping with the help of an adversarial loss which encourages synthetic CT images to look like real CT images. A second CNN is used to map the synthetic CT back to the MR domain, and a cycle-consistency loss forces this reconstructed image to match input MR image.

However, cycleGAN cannot guarantee the structural consistency between synthetic and input images due to the lack of direct constraints between these two images. As shown in Fig. 1, the reconstructed MR image is almost identical to the input MR image, indicating that cycle consistency is maintained, but the synthetic CT image is quite different from the ground truth, especially in skull region. This shows that the structure of the synthetic CT image is not consistent with that of the input MR image. To overcome this, Zhang *et al.* [17] used an extra loss to force the segmentation of synthetic image to be the same as input image by training two auxiliary segmentation networks. This requires a training dataset with

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Cellular carbon microstructures developed by using stereolithography

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ABSTRACT

Additive manufacturing has attracted much attention to generate structures containing ordered cells and customized shapes with various materials. A simple method was proposed to develop net-shape cellular carbon microstructures (CCMs) with controllable low shrinkage by using stereolithography. The polymer architectures, made of photosensitive resins, and sodium chloride were directly used as carbon precursors and granular support during carbonization, respectively. In addition, graphite powder was introduced into the granular support, which significantly enhances the mechanical property and electrical conductivity of the CCMs, and low graphite content has no significant effect on the volume shrinkage. The extremely high-porosity CCMs without distortion and breakage were obtained, showing controllable low volume shrinkage (44%–52%) with extremely low carbon yield (6%). The microstructure, mechanical property and electrical conductivity were measured and compared. It was found that the CCMs with graphite particles attaching on their surfaces show smooth surfaces with fewer defects, and possess great mechanical property (compressive stress and elastic modulus are 0.36 Mpa and 23.9 Mpa, respectively) and electrical conductivity (0.43 S/cm), which makes them promising materials for many potential applications.

1. Introduction

Porous carbon structures, noted as carbon foams, have found many applications including catalyst materials for chemical reactions [1], containers for thermal energy storage [2–4], electrode materials for batteries [5,6], materials for electromagnetic shielding [7], absorbers for organic solvents [8,9]. This is attributed to the distinctive and excellent properties of carbon foams, e.g. light weight, high interconnected porosity, good thermal and electrical conductivity and hydrophobic property.

In most cases, carbon foams can be classified into graphitic and glassy types based on graphitization degree. As reported in the literature [10], the preparation processes of carbon foams, despite graphitic or glassy, mainly include foaming with carbonization, template carbonization and others. Many graphitic carbon foams were produced by applying foaming method on coal, coal tar pitch and petroleum pitch, which have good mechanical property, good thermal and electrical conductivities, but low porosity and uncontrollable random cells [11–13]. There is an increasing interest in preparing highly porous carbon foams with random cells by polyurethane (PU)-template method with various precursors (e.g. phenol or resorcinol-formaldehyde resin [3,14–16], furfural resin [17], polyimide [18] and pitch-based materials [19,20]). Furthermore, several researchers reported simple methods to fabricate carbon foams by direct carbonization of melamine foams which have extremely low density and high porosity [8,9]. However, high shrinkage and deformation appear due to the low carbon yield of melamine (~9%). All these random carbon foams result in some beneficial properties, however, some disadvantages may occur, like uncontrollable macro shapes, random cell structure, even high shrinkage and deformation.

It has been shown that the material utilization and properties can be dramatically improved by introducing ordered cells [21,22] which can be easily fabricated by using additive manufacturing. However, only a limited number of investigations regard to the preparation of carbon cellular structures by using additive-manufactured polymer structures in recent years. This is due to the fact that the polymers applied to additive manufacturing are mostly thermoplastic, or have a considerable weight loss during carbonization, like the photosensitive resins [23]. A. Szczurek et al. [24] attempted to develop carbon periodic cellular structures under hydrothermal conditions by using 3D-printed polymer

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Plasma-activated thermosensitive biogel as an exogenous ROS carrier for post-surgical treatment of cancer

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ABSTRACT

Post-surgical residual tumor cells are the primary cause of relapse and progression of cancer but unfortunately, there are limited therapeutic options. In this work, a fillable plasma-activated biogel is produced on a thermosensitive biogel [(Poly-DL-lactide)-(poly-ethylene glycol)-(poly-DL-lactide), PLEL] with the aid of a discharge plasma for local post-operative treatment of cancer. *In vivo* data show that the plasma-activated PLEL biogel (PAPB) eliminates residual tumor tissues after removal surgery and also inhibits *in situ* recurrence while showing no evident systemic toxicity. Moreover, the PAPB possesses excellent storage capability, allows for slow release of plasma-generated reactive oxygen species (ROS), and exhibits good ROS-mediated anticancer effects *in vitro*. Our results reveal that the novel plasma-activated biogel is an effective therapeutic agent for local post-operative treatment of cancer.

1. Introduction

Surgery is the preferred means to treat most cancers but its success hinges on the extent of tumor resection [1,2], and post-surgical residual cancer cells constitute the primary reason for the failure of surgical treatments. To improve the efficiency of cancer therapy, chemotherapy or radiotherapy is often performed after surgery but serious side effects and complications may arise [3,4]. Although chemotherapy or radiotherapy can eliminate most post-surgical residual cancer cells, the drug-resistant and radio-resistant cells left behind can cause *in situ* tumor recurrence and even cancer metastasis. Normally, these residual post-surgical cancer cells are concentrated primarily at the operation location before relapse and progression of cancer [5]. In this respect, new treatments against local post-surgical residual tumor cells (tissues) besides chemotherapy and radiotherapy are highly desirable.

Cold atmospheric pressure plasma technology is a viable cancer therapy in which oxidative stress in the target cancerous tissues are triggered without thermal damage [6,7]. Recent studies on the use of plasmas for cancer therapy demonstrate that plasma irradiation with the proper dose can kill cancer cells selectively but pose little deleterious effects on normal cells [8,9]. Furthermore, the clinical antitumor efficacy in patients suffering from head and neck cancer suggests that the plasma treatment is an effective strategy in oncology [10,11]. The primary effects induced by plasmas are generation and delivery of reactive oxygen species (ROS, such as H_2O_2, O_3, $OH\bullet$, NO_x^-, O_2^-, $ONOO^-$/ONOOH) [7,9]. Generally, ROS at low concentrations mediate multiple cellular signaling pathways and metabolic processes but show cellular toxicity at high concentrations [12]. It is well known that cancer cells produce ROS *via* their abnormally active metabolism resulting in a higher level of endogenous ROS in cancer cells compared to normal cells [13,14]. The higher endogenous ROS levels cause cancer cells to reach the lethal threshold sooner, while the stress induced by plasma-triggered ROS is tolerable in normal cells [15]. However, despite the promising anticancer effects, clinical adoption of plasma technology still faces several hurdles. First of all, the penetration depth of plasmas in tissues is usually less than 1 mm [16,17] and therefore, a supplementary surgical treatment is usually necessary because these deeper tumor cells cannot be irradiated directly [18]. Secondly, although the use of

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Nanoscale Surface Topography Reduces Focal Adhesions and Cell Stiffness by Enhancing Integrin Endocytosis

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Abstract

Both substrate stiffness and surface topography regulate cell behavior through mechanotransduction signaling pathways. Such intertwined effects suggest that engineered surface topographies might substitute or cancel the effects of substrate stiffness in biomedical applications. However, the mechanisms by which cells recognize topographical features are not fully understood. Here we demonstrate that the presence of nanotopography drastically alters cell behavior such that neurons and stem cells cultured on rigid glass substrates behave as if they were on soft hydrogels. With atomic force microscopy, we show that rigid nanotopography resembles the effects of soft hydrogels in reducing cell stiffness and membrane tension. Further, we reveal that nanotopography reduces focal adhesions and cell stiffness by enhancing the endocytosis and the subsequent removal of integrin receptors. This mechanistic understanding will support the rational design of nanotopography that directs cells on rigid materials to behave as if they were on soft ones.

Graphical Abstract

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Author Contributions

B.C., X.L., and L.H.K. conceived the study and designed experiments. X.L., B.C., L.H.K., and T.L.L. wrote the manuscript. X.L. and Z.J. fabricated nanostructures. L.H.K. and C.T. prepared hydrogels. X.L., L.H.K., and W.Z. performed most biological experiments. L.H.K., C.T., and Z.J. performed the bioprinting experiment. X.L. and B.C. designed the software programs for data analysis. All authors discussed the results and commented on the manuscript.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.nanolett.1c01934.
Nanofabrication and surface functionalization of nanopillar quartz substrates, preparation and surface functionalization of polyacrylamide hydrogels, cell culture, isolation, and culture of hippocampal neurons, staining and imaging of hippocampal neurons, differentiation of stem cells, staining and imaging of stem cells, AFM measurement, staining and imaging of cell area and YAP, bioprinting, staining imaging of focal adhesions and stress fibers, imaging of total endocytosis, temperature-mediated endocytosis inhibition, and drug-induced endocytosis inhibition (PDF)

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Targeting and Covalently Immobilizing the EGFR through SNAP-Tag Technology for Screening Drug Leads

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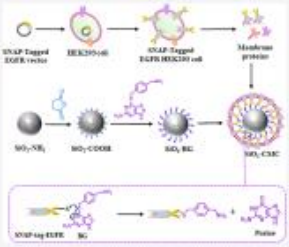
ABSTRACT: Membrane protein immobilization is particularly significant in in vitro drug screening and determining drug−receptor interactions. However, there are still some problems in the immobilization of membrane proteins with controllable direction and high conformational stability, activity, and specificity. Cell membrane chromatography (CMC) retains the complete biological structure of membrane proteins. However, conventional CMC has the limitation of poor stability, which results in its limited life span and low reproducibility. To overcome this limitation, we propose a method for the specific covalent immobilization of membrane proteins in cell membranes. We used the SNAP-tag as an immobilization tag fused to the epidermal growth factor receptor (EGFR), and Cys145 located at the active site of the SNAP-tag reacted with the benzyl group of O^6-benzylguanine (BG). The SNAP-tagged EGFR was expressed in HEK293 cells. We captured the SNAP-tagged EGFR from the cell membrane suspension onto a BG-derivative-modified silica gel. Our immobilization strategy improved the life span and specificity of CMC and minimized loss of activity and nonspecific attachment of proteins. Next, a SNAP-tagged EGFR/CMC online HPLC-IT-TOF-MS system was established to screen EGFR antagonists from *Epimedii folium*. Icariin, magnoflorine, epimedin B, and epimedin C were retained in this model, and pharmacological assays revealed that magnoflorine could inhibit cancer cell growth by targeting the EGFR. This EGFR immobilization method may open up possibilities for the immobilization of other membrane proteins and has the potential to serve as a useful platform for screening receptor-binding leads from natural medicinal herbs.



Efficient screening of active ingredients is currently recognized as a key constraint in the research and development of high-efficiency drug leads. Lead compounds in natural drugs, such as those used in traditional Chinese medicine, have received considerable research attention; rapid screening and identification of biologically active components from natural products remain a technical challenge.[1−3] High-throughput screening of active ingredients with their sources has become a challenging scientific problem in this field. Membrane proteins are major targets for drug discovery and development.[4] Among the currently marketed drugs, about 50−60% of drugs use membrane proteins to exert their effects.[5−7] However, there are still many challenges in discovering drugs that target membrane receptors. Importantly, the limited availability of effective methods for screening drug−protein interactions hinders the discovery of potential drug candidates.

Bio-affinity chromatography targeting enzymes, receptors, cell membranes, and antigens is an important method for screening the active ingredients of drugs.[8−12] Among these methods, the major challenge of affinity screening technology is the requirement of protein targets with high purity, activity, and high stability;[13] this is because obtaining a stable, active membrane protein is markedly difficult. In receptor chromatography, membrane proteins leave the lipid environment,[14] affecting their activity to some extent. Contrastingly, cell membrane chromatography (CMC) maintains the activity of the receptors on the cell membrane.[15] CMC is a type of bio-affinity chromatography, in which the cell membrane stationary phase (CMSP) is prepared by immobilizing cell membranes containing special receptors on silica.[16−20] As unique natural biomaterials, cell membranes are superior to synthetic biopolymers and single biological macromolecules in many aspects because they have a complete biological structure and a complex interface and cannot be easily replicated in other ways. Typically, the binding force between the cell membrane and silica gel in the CMC model is hydrophobic interaction.[21−23] With the use of a CMC column, the cell membrane gradually detaches from the silica gel, resulting in a short life span and low efficiency.[24−28] Therefore, the method

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Mechanics-driven nuclear localization of YAP can be reversed by N-cadherin ligation in mesenchymal stem cells

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Mesenchymal stem cells adopt differentiation pathways based upon cumulative effects of mechanosensing. A cell's mechanical microenvironment changes substantially over the course of development, beginning from the early stages in which cells are typically surrounded by other cells and continuing through later stages in which cells are typically surrounded by extracellular matrix. How cells erase the memory of some of these mechanical microenvironments while locking in memory of others is unknown. Here, we develop a material and culture system for modifying and measuring the degree to which cells retain cumulative effects of mechanosensing. Using this system, we discover that effects of the RGD adhesive motif of fibronectin (representative of extracellular matrix), known to impart what is often termed "mechanical memory" in mesenchymal stem cells via nuclear YAP localization, are erased by the HAVDI adhesive motif of the N-cadherin (representative of cell-cell contacts). These effects can be explained by a motor clutch model that relates cellular traction force, nuclear deformation, and resulting nuclear YAP re-localization. Results demonstrate that controlled storage and removal of proteins associated with mechanical memory in mesenchymal stem cells is possible through defined and programmable material systems.

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Variational HyperAdam: A Meta-Learning Approach to Network Training

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Abstract—Stochastic optimization algorithms have been popular for training deep neural networks. Recently, there emerges a new approach of learning-based optimizer, which has achieved promising performance for training neural networks. However, these black-box learning-based optimizers do not fully take advantage of the experience in human-designed optimizers and heavily rely on learning from meta-training tasks, therefore have limited generalization ability. In this paper, we propose a novel optimizer, dubbed as Variational HyperAdam, which is based on a parametric generalized Adam algorithm, i.e., HyperAdam, in a variational framework. With Variational HyperAdam as optimizer for training neural network, the parameter update vector of the neural network at each training step is considered as random variable, whose approximate posterior distribution given the training data and current network parameter vector is predicted by Variational HyperAdam. The parameter update vector for network training is sampled from this approximate posterior distribution. Specifically, in Variational HyperAdam, we design a learnable generalized Adam algorithm for estimating expectation, paired with a VarBlock for estimating the variance of the approximate posterior distribution of parameter update vector. The Variational HyperAdam is learned in a meta-learning approach with meta-training loss derived by variational inference. Experiments verify that the learned Variational HyperAdam achieved state-of-the-art network training performance for various types of networks on different datasets, such as multilayer perceptron, CNN, LSTM and ResNet.

Index Terms—Network training, meta-learning, learning to optimize, variational inference, variational hyperadam

1 Introduction

In recent years, we have witnessed the powerful capability of deep learning approach in feature learning [1], [2], distribution estimation [3], etc. Deep learning not only achieved impressive performance in various research areas, such as image analysis [4], [5], [6], speech recognition [7], robotics [8], but also attracted extensive attentions from industry for incorporation into products.

Training deep neural networks is an important task in deep learning research. It requires the network optimizer to be generalizable to different datasets and varying network architectures, e.g., network type, depth, width, activation functions, etc. Specifically, given a network $f(\cdot, w)$, the aim of network training is to find the optimal network parameter vector w^* by minimizing the empirical loss on the training dataset $\mathcal{D}$:

$$w^* = \arg\min_{w} \sum_{(x,y)\in\mathcal{D}} l(f(x, w), y), \tag{1}$$

where $l(\cdot,\cdot)$ is the loss function and x is training data with label y in $\mathcal{D}$. For deep neural networks, the training loss is highly non-convex, and the numbers of network parameters and training data are commonly large. These characteristics bring challenges on designing an effective optimizer for network training.

In this paper, we denote the network to be trained as *learner*, the training loss of the learner as *optimizee*. The network training algorithm is dubbed as *optimizer*, which is used to optimize the network parameter of the learner by minimizing its corresponding optimizee. The gradient-based optimizer can be regarded as a function O that maps the gradient g_t to the network parameter update vector d_t at the tth training step:

$$d_t(\boldsymbol{\Theta}) = O(g_t, \mathcal{H}_t, \boldsymbol{\Theta}), \tag{2}$$

where $\mathcal{H}_t$ represents the historical gradient information, such as $\mathbb{E}(g_t)$ and $\mathbb{E}(g_t^2)$, and $\boldsymbol{\Theta}$ represents parameters of the optimizer, including but not limited to the learning rate.

Traditionally, stochastic gradient descent (SGD) [9] and its variants, such as Momentum [10], RMSProp [11], AdaGrad [12], AdaDelta [13] and Adam [14], are the most popular optimizers with good generalization ability to various network architectures and datasets. Unlike SGD, Momentum [10] takes the historical gradient information into consideration in designing the parameter updating rule. RMSprop, AdaGrad, AdaDelta and Adam are designed with adaptive learning rates. Among them, Adam is widely used in network training, and it takes the unbiased estimation of second moment of gradient to act as adaptive learning rate. However, this may introduce additional hyperparameters, e.g., exponential decay rates β, γ in

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A one-pot CRISPR/Cas13a-based contamination-free biosensor for low-cost and rapid nucleic acid diagnostics

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ABSTRACT

The pandemic due to the outbreak of 2019 coronavirus disease (COVID-19) caused by novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has raised significant public health concerns. Rapid, affordable, and accurate diagnostic testing not only paves the way for the effective treatment of diseases, but also plays a crucial role in preventing the spreading of infectious diseases. Herein, a one-pot CRISPR/Cas13a-based visual biosensor was proposed and developed for the rapid and low-cost nucleic acid detection. By combining Cas13a cleavage and Recombinase Polymerase Amplification (RPA) in a one-pot reaction in a disposable tube-in-tube vessel, amplicon contamination could be completely avoided. The RPA reaction is carried out in the inner tube containing two hydrophobic holes at the bottom. After the completion of amplification reaction, the reaction solution enters the outer tube containing pre-stored Cas13a reagent under the action of centrifugation or shaking. Inner and outer tubes are combined to form an independent reaction pot to complete the nucleic acid detection without opening the lid. This newly developed nucleic acid detection method not only meets the need of rapid nucleic acid detection at home without the need for any specialized equipment, but also fulfils the requirement of rapid on-site nucleic acid detection with the aid of small automated instruments. In this study, CRISPR/Cas13a and CRISPR/Cas12a were used to verify the reliability of the developed one-pot nucleic acid detection method. The performance of the system was verified by detecting the DNA virus, i.e., African swine fever virus (ASFV) and the RNA virus, i.e., SARS-Cov-2. The results indicate that the proposed method possesses a limit of detection of 3 copy/μL. The negative and positive test results are consistent with the results of real-time fluorescence quantitative polymerase chain reaction (PCR), but the time required is shorter and the cost is lower. Thus, this study makes this method available in resource-limited areas for the purpose of large-scale screening and in case of epidemic outbreak.

1. Introduction

Frequent and large-scale infectious diseases exhibit a significant performance impact on the social stability and economic development, leading to the international or regional health crises. In particular, coronavirus disease (COVID-2019), which broke out at the end of 2019, has spread in more than 200 countries around the world, with more than 250 million confirmed cases (Sieber et al., 2021). Almost all infectious diseases are caused by nucleic acid pathogens (except in rare cases such as prions); therefore, pathogen-specific nucleic acids (RNA or DNA) are often used as the "gold standard" biomarker for the diagnosis of infectious diseases. Sensitive, distinctive, and rapid diagnostic testing not only paves the way for effective treatment of diseases, but also plays a crucial role in preventing the spreading of infectious diseases (Wei et al., 2021). The current epidemic of COVID-2019 is fierce with high infection rates and high requirements for the turnover of nucleic acid detection. Moreover, the strong latent characteristics of COVID-2019 indicate that highly sensitive rapid diagnosis and on-site screening of suspected patients and close contacts need to be carried out in communities, ports, and other places.

To meet the requirements of detection sensitivity and throughput analysis, the currently available diagnostic methods, e.g., real-time fluorescence quantitative PCR, are time consuming and require expensive laboratory settings and well-trained personnel (Mukama et al., 2020a). The existing rapid nucleic acid detection equipment based on microfluidics and PCR technology, such as GeneXpert, Filmarray, and other systems, have high testing cost (the cost of a single test is 100–500 $). Therefore, such tests are not available in resource-limited areas, for

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Viewpoint

Expert consensus on magnetic recanalization technique for biliary anastomotic strictures after liver transplantation

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Biliary anastomotic stricture (BAS) is a common complication after liver transplantation.

Endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangial drainage (PTCD) is the preferred treatment for BAS. However, these methods are helpless for completely occluded strictures. Magnetic recanalization technology (MRT), which is an application of magnetic compression anastomosis, is reported as a revolutionary way to treat BAS, and initially imply a satisfactory result for complicated cases (1-7). However, there are still no consensus reported. On the Third International Conference of Magnetic Surgery held in Xi'an, experts from various countries have discussed associated fields of MRT in treating BAS and achieved the following consensus.

Indications and contraindications of MRT

Indications

(I) Biliary anastomotic occlusion, such as bilo-biliary anastomosis and bilo-enteric anastomosis;
(II) Refractory stricture with multiple failures of ERCP or PTCD;
(III) Two biliary stricture stumps are close to the same axis.

Absolute contraindications

(I) The stricture length is >20 mm;
(II) A large amount of ascites or severe coagulation dysfunction, which do not allow an effective PTCD to be established;

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