Review

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Harnessing magnetic-mechano actuation in regenerative medicine and tissue engineering

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Mechanical stimulus is of upmost importance in tissues developmental and regeneration processes as well as in maintaining body homeostasis. Classical physiological reactions encompass an increase of blood vessel diameter upon exposure to high blood pressure, or the expansion of cortical bone after continuous high-impact exercise. At a cellular level, it is well established that extracellular stiffness, topography, and remote magnetic actuation are instructive mechanical signals for stem cell differentiation. Based on this, biomaterials and their properties can be designed to act as true stem cell regulators, eventually leading to important advances in conventional tissue engineering techniques. This review identifies the latest advances and tremendous potential of magnetic actuation within the scope of regenerative medicine and tissue engineering.

Mechanotransduction, magnetic actuation and tissue engineering – connecting the dots

Mechanical forces exert epigenetic control in tissue developmental, remodelling, and regeneration processes [1,2]. The first medical evidence of the role of mechanical forces in tissue remodelling was provided by the German surgeon Jullius Wolff >100 years ago after detailing the influence of mechanical load on bone mass and geometry in his study 'The Law of Bone Transformation' [3]. Striking evidence of the impact of mechanical loading on bone remodelling came from astronauts living under microgravity conditions. Lack of mechanical load led to detrimental effects such as a significant loss of bone mass, higher incidence of cardiovascular disease, and signs of accelerated biological ageing [4]. Increased mechanical load can, in contrast, have positive effects, as is the case for high-performance athletes such as Olympic fencers. These athletes undertake intermittent high-impact activity, leading to expansion of cortical bone, as well as increase of trabecular bone density and muscle mass [5]. Such strengthening is vital for the protection of the body from injuries [6].

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Physiological changes in response to mechanical load are initiated by a process called mechanotransduction, in which cells detect mechanical changes in their microenvironment through specialised machinery and then translate the information into an appropriate biological response. Mechanotransduction is mediated by structural proteins such as integrins and actomyosin fibres, which establish a physical connection between the cell and the microenvironment. When a mechanical stimulus is applied to the cell, the increase in tension is transmitted through the contraction of actomyosin fibres, a process mediated by the small GTPase Rho and Rho-associated protein kinase (ROCK) proteins [7].

Mechanotransduction is pivotal in tissue homeostasis; however, ageing and disease may impair this physiological process, giving rise to musculoskeletal disorders [8–14], in particular, the loss of muscle mass and function, decreased

Glossary

Actomyosin: actin and myosin fibres present in the cytoskeleton.
Emerin: a protein of the inner nuclear envelope.
Integrins: transmembrane proteins that convey forces inside and out of the cell and activate downstream signalling pathways mediated by the establishment of large integrin-scaffold protein assemblies called focal adhesions.
iPS cells: induced pluripotent stem cells obtained from adult cells, through genetic reprograming.
Magnetic actuation: technique of activating mechanotransduction signalling pathways in cells through the application of magnetic force. The established field can be static being the force constant, or oscillating showing a pulsed behaviour. Activation of mechanotransduction signalling pathways can occur within minutes.
Magnetic bioreactor: magnetic array capable of delivering an oscillating magnetic field to cells growing in standard tissue culture surfaces or biomaterials. Although the frequency is tunable, values often range between 1 and 3 Hz, which are the closest to physiological stress.
Mechanical cues: physical stimulus present in the cell microenvironment.
PEMF therapy: delivery of pulsed magnetic force for healing purposes, for example, to bridge a non- or delayed bone fracture.
Reverse piezoelectric effect: mechanical deformation caused by an electrical field.
Rho-GTPases: small signalling G proteins implicated in numerous cells processes such as cytoskeleton dynamics.
Scaffold: structures from natural of synthetic origin that provides cells physical support and guidance.
SPIONs: iron oxide nanoparticles with supermagnetic properties used in stem cell guidance and magnetic resonance.
Stem cell: undifferentiated cell with the potential of generating several specialised cell lineages.
Stretch-activated ion channels: ion channels gated in response to alterations of the conformation of the cytoplasm membrane.
Tissue graft: tissue portion from autologous, allogeneic or xenogeneic source, employed to repair damaged tissue.
Tissue engineering: use of a combination of materials, cells, active molecules and engineering principles to restore the biological function of a damaged tissue or organ.

healing capacity, [15], and osteoporosis [16,17]. The fact that osteoporosis is aggravated in menopause, during which oestrogen levels are reduced, may in part be explained by the role of oestrogen as a mechanosensitiser hormone [8]. Sustaining physiological mechanotransduction is thus crucial for maintaining tissue homeostasis and preventing musculoskeletal disorders.

An effective strategy for improving or sustaining mechanotransduction is magnetic actuation (see Glossary), which has been available for nearly three decades in the form of FDA-approved pulsed electromagnetic field (PEMF) therapy [18]. Owing to recent progress in nanomedicine and molecular biology, we can begin to understand the signalling pathways involved in mechanotransduction and exploit them with magnetic actuation for a myriad of applications: stem cell differentiation and homing to injury sites, as well as tissue engineering strategies [19–25]. In tissue engineering, magnetic actuation can allow for better seeding in 3D scaffolds [26–28], and can be used in scaffold-free approaches to build tissues bottom-up from mesenchymal stem cells (MSCs) or induced pluripotent stem cells (iPSCs) [29–31].

We discuss the fundamentals of mechanotransduction, the potential use of magnetic actuation in stem cell differentiation and in several aspects of tissue engineering, focusing on the musculoskeletal system, given its vulnerability to physical strain, and because musculoskeletal disorders are predicted to rise due to an increase of the ageing population and extension of life expectancy [32,33]. Understanding mechanotransduction and identifying the potential uses of magnetic actuation will open new and vibrant avenues for musculoskeletal tissue engineering and regenerative medicine strategies.

Box 1. Overview of proteins involved in mechanotransduction

Focal adhesion (FA) signalling, actomyosin contraction, stretch-activated ion channels, and nuclear associated proteins [26] are all important for mechanotransduction (Figure I). Of pivotal importance are integrins, transmembrane heterodimers proteins composed of α and β subunits that physically couple the ECM to the cytoskeleton by linker proteins such as talin and vinculin [27]. The cytoskeleton, composed of actin and myosin fibres, physically bridges the ECM or the cell membrane to the nucleus. Although the nucleus is the largest and stiffest organelle in the cell, it is still susceptible to mechanical forces conveyed through the cytoskeleton [28]. In the nucleus, lamins, transcription regulators Yes-associated protein and tafazzin (YAP/TAZ), myocardin-related transcription factor A (MRTF-A) and nuclear factor (NF)-κB all participate in gene regulation triggered by mechanical cues [29,30].

Integrins convey forces between inside and outside the cell and activate downstream signalling pathways. This mechanotransduction is made possible by the establishment of large integrin–scaffold protein assemblies called FAs. Besides integrins, cells can perceive external mechanical stimuli through many other proteins such as cadherins, catenins, the components of the cytoskeleton and nucleoskeleton, stretch-activated ion-channels, and growth factor receptors. Similar to integrins, cadherins are transmembrane proteins and important signalling hubs, but instead of linking the ECM to the cell, they mediate cell–cell communication. In classical cadherins, the cytoplasmic motif is linked to β-catenin. However, because β-catenin is also implicated in transcriptional processes, it may be translocated from cadherins to the nucleus in response to intracellular tension, mediated by signalling components such as the small GTPase Rho and ROCK.

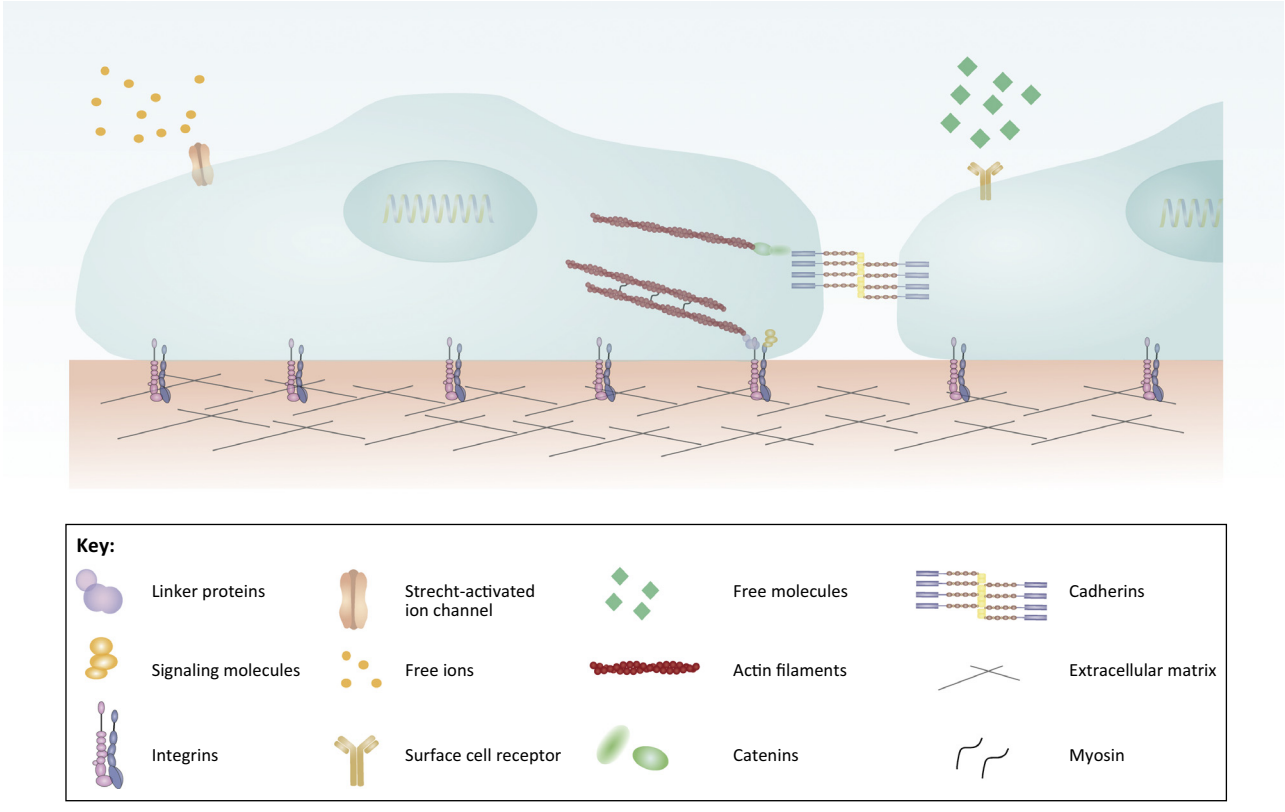

Figure I. Overview of mechanotransduction mediators in a cell.