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Review Article

Mechanotransduction; Comparing Four Mechanical Forces

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Abstract

Physical forces affect homeostasis. The recent advances in molecular techniques and tissue assays allowed the science to measure these effects at the level of proteins, growth factors, and gene expression. In this short review, we report the experimental work done by molecular biologists with regard to the molecular changes in response to four different types of physical stimuli: stretch, fluid flow, fluid pressure, and negative pressure.

Abbreviations

Ang-2: Angiogenin type 2; a vascular growth factor.
INP: Intermittent negative pressure.
FAK: Focal adhesion kinase.
MSCs: Mesenchymal stem cells.
PDGF- ββ: Platelet-derived growth factor beta-beta.
Rac-1: Ras-related C3 botulinum toxin substrate 1 (a cell cycle regulatory pathway).
Ras: A signaling protein; (discovered in rat sarcomas)

Introduction

Cells could divide, differentiate, transfer, or even die in response to physical stimulus, and the improper response to these stimuli leads to pathologies [1]. For an organism to survive, it should pass the test of adaptation to physical forces [2]. The strategy to and magnitude of this response differs from an organism to another, and the difference is more obvious when comparing unicellular organisms to multi-cellular organisms [3]. When the mechanical stimulus is translated into a chemical cell signal, the process is called mechanotransduction [4,5,6]. The molecular pathways that represent the response cascade to mechanical power are referred to as mechanosensing pathways. Various mechanical forces had been tested to study their effects on the living tissues, and these include: mechanical stretch, fluid flow, fluid pressure, and negative pressure.

Mechanical Stretch

Studies showed that tissues and cells could be stimulated to grow faster *in vitro* when subjected to a suitable stretch power, as documented by Powell *et al* on engineered skin [7], and Lee *et al* on organ culture arteries [8]. Yung *et al* (2009) demonstrated the effect of stretch on vessels by applying cyclical strain on human umbilical vein; it did activate vascular growth factors production and the expression of the cytokines (Ang-2) and (PDGF-ββ) [9]. A good target for biomechanical stimulation is mesenchymal cells, because they are capable to differentiate into many types of cells [10,11]. Aiming to produce cardiac smooth muscle tissue, Park *et al* searched on (2004) the possibility of giving rise to smooth muscle cells from the mesenchymal stem cells (MSCs) of the bone marrow [10]. They concluded that strain on one direction could induce smooth muscle differentiation from bone marrow mesenchyme, unlike multidirectional straining, which gave a disappointing result [10]. Also in (2004), Hamilton, Maul, and Vorp explained the possibility of harvesting smooth muscle cells from progenitor cells of rat's bone marrows through cyclic strain; daughter cells were well aligned and expressed smooth muscle cells Actin filaments [12]. Nieponice *et al* concluded on (2007) that cyclic stretch further accelerated the conversion of bone marrow progenitor cells into smooth muscle cells, smooth muscle markers were up-regulated, and Collagen amount rose [13]. In (2008), Zhang *et al* concluded, through experiments on rat bone mesenchymal cells, that stretch to one direction increases the expression of type I and type III collagens; the most abundant collagens [11], and Tenascin-C protein; an extracellular matrix glycoprotein protein that modulates cell adhesion and morphology [11,14]. Cells of mesenchyme also gained a more elongated figure [11]. A remarkable comparative study was performed by Maul *et al* in (2011); it compared the effects of cyclic stretch, cyclic hydrostatic pressure, and laminar shear stress on mesenchymal stem cells [15]. Results confirmed that the mechanical cues could change the shape of mesenchymal cells, affect their size, and modify their configuration [15]. Cyclic stretch, in particular, leads to the expression of smooth muscle cell proteins markers and muscle genes, while the hydrostatic pressure and the shearing stress were in favor of activating endothelium genes [15].

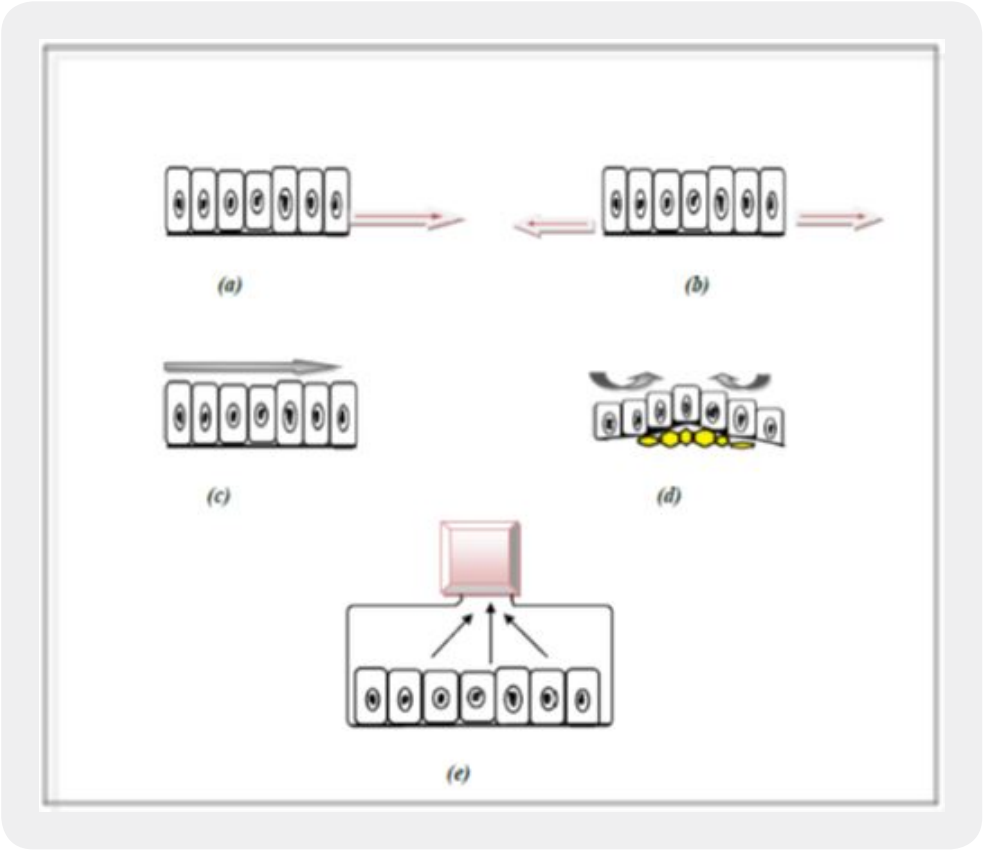

Figure: *A diagram representing mode of stretch in one direction (a), two directions (b), laminar fluid flow (c), disturbed flow due to an atherosclerotic plaque (d), and the INP model (e), where the pink box resembling the negative pressure source.*

Fluid Flow

The mechanotransduction in the vascular cells; endothelial cells, fibroblasts, and smooth muscle cells, and their coordination to maintain an optimum vascular function, was researched in details [16]. Shear stress gives the endothelial cells a spindle shape and a well organized manner at the same direction of the stream [15,16]. It shifts the smooth muscle cells into the protein synthesis pathways [16]. Ting *et al* (2012) stated that regular laminar flow gives rise to bigger cell junctions when compared to a disorganized flow medium and the structural proteins are organized parallel to the current direction [17]. Literature revealed that cellular responses to abnormal hydro-mechanical conditions are fundamental in the etiology of atherosclerosis [18,19]. The normal blood flow inhibits pro-inflammatory mediators, while the disturbed, plaque-mediated flow does not; hence leukocytes-mediated inflammatory response occurs and progresses into the fully developed atherosclerotic vessel, and the smooth muscles thin out because they are not stimulated by cyclic stretch, which is masked due to the preformed plaque [18].

Fluid Pressure

A mechanical stimulation particularly related to the bladder is the cyclic hydrodynamic pressure. The process of emptying and refilling of the bladder has its role in proliferation and preservation of the function of smooth muscle cells of the bladder. Wu *et al* (2012) researched, on a cell culture, the activity status of the Rac-1 cellular signaling pathway, which is an important pathway in cell division control [20]. Results showed that Rac-1 was activated in response to the hydrodynamic pressure, among other Protein kinases, and the smooth muscles of the bladder cells were dividing in a remarkably accelerated manner [20]. Wei *et al* examined, in (2014), the protein Integrin's role in the proliferation of bladder smooth muscle cells in a hydrodynamic pressure medium [21]. Integrin is a signal mediator of growth and proliferation, amongst many other cellular modulating functions [22]. The cyclic hydrodynamic pressure had lead to activation of cell division, induction of the synthesis of Integrin, and phosphorylation of focal adhesion kinase-FAK, the main regulator of Integrin-dependent pathways [21]. Recently in (2017), Chen *et al* studied bladder tissues responses to another mechanical stimulus; stretch, and they targeted mainly the extracellular matrix (ECM) proteins [23]. Results showed that expression of collagens I and III were up-regulated, and the FAK-dependent Integrin pathway is presumed to be a responsible factor [23].

Negative Pressure

It is simply defined as a pressure less than the normal atmosphere. It is found normally in the body at the lung, as an important factor for respiration [24]. At the tissue level, there were few trials to document the effects of negative pressure in the sub-cellular and molecular level. Zhang *et al* (2010) worked on MSCs and studied how intermittent negative pressure, (INP), could determine their offspring and velocity of division [25]. They applied a half an hour INP of low magnitude; unexpectedly, cell division was inhibited, apoptosis (programmed cell death), was higher than usual, and collagen-I was over-expressed [25]. On 2014, Yang *et al* operated a similar study on MSCs, and concluded that cells shifted toward apoptosis, over-expressed type I collagen and alkaline phosphatase (ALP), and activated osteoblast formation [26]. Sun *et al* (2017) studied the possible effect of INP in accelerating the healing on a post-operative anterior cruciate ligament in a rabbit [27]. The experiment showed accelerated osteogenesis and reduction in the inflammatory markers TNF-α and IL-1β in the group underwent INP. The study supported that INP could promote the healing at the junction of bone and tendon [27].

Discussion

From the above studies, it is obvious that mechanical forces are generally in favor of tissue growth enhancement and proliferation, with the exception of negative pressure which had explicitly induced cellular death. Stretch power proved to enhance selective differentiation of MSCs, particularly to smooth muscle cell type. Stretch mechanics is a promising method in the skin graft and wound management. The regular vascular flow maintains the shape and alignment of the vascular endothelium, in contrast to the disrupted flow, which favors the formation of plaques and, consequently, atherosclerosis. Maintaining the straight flow is protective against thromboembolic phenomenon. Fluid pressure proved to augment the bladder epithelial proliferation, and expression of Integrins. It is fair to say that the above three mechanical factors promote

tissue proliferation and maintenance, the stretch force being the most potent modality. Negative pressure, on the other hand, gave paradoxical outcome, being in favor of apoptosis and, at the same time, fastening wound healing and promoting collagen expression. Negative pressure, apart from the respiratory mechanics, is not a normally occurring physical phenomenon, while fluid and stretch mechanics are concomitant with the biological processes. Scientists tend to use INP in their trials rather than the use of sustained negative pressure. This is basically to avoid the accumulation of fluid and inflammatory cells. A couple of researches were performed in cancer cells with regard of INP effect in the growth inhibition, two results were in favor of apoptosis [25,26], and one stated that malignant cells became more aggressive [28]. Negative pressure use will be beneficial in chronic wounds management, burn scar management, and cancer studies, particularly skin cancer.

Conclusion

Physical powers; stretch, fluid flow, hydrostatic pressure and negative pressure, affect cellular proliferation, protein expression, and tissue configuration. The outcome of these powers ranges between tissue proliferation enhancement and cell death. INP might have an impact in Cancer treatment studies.

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