Physiology involves regenerative strategies, where injury and repair are an essential part of our normal existence and are necessary for us to survive within our environment. Regenerative strategies involve dynamic processes characterized by cell migration along extracellular highways formed by protein matrices secreted by the cells themselves. This issue of Physiology explores the dynamic world of physiologically based regenerative strategies for life.

Recent research suggests that both chemical and physical cues within the cellular microenvironment guide cell migration. In their review (5), Vedula and colleagues explore new mechanistic insights into cell migration provided by advanced technologies in microscopy and microfabrication, and the ability to quantify the spatio-temporal distribution of forces exerted at the cell-substrate and cell-to-cell interface within migrating monolayers. They show that cells can not only sense the presence of their neighbors but also modify their behavior accordingly. Hence, understanding the various mechanisms governing collective cell behavior is necessary to better characterize the physiological processes of cell migration. However, it remains unclear how multicellular clusters process information from a variety of stimuli and reach a consensus. Identifying the contribution of mechanical and physical cues and the manner in which they interact with each other to regulate collective cell behavior can aid the development of novel strategies to modulate specific biological processes, such as accelerating wound healing or retarding cancer metastasis.

Fibroblasts are cells that secrete and maintain the extracellular matrix throughout the body. Fibroblast migration is essential for normal wound healing, and fibroblasts contribute to pathological matrix deposition in fibrosis. In his review, Tschumperlin (4) summarizes current understanding of how fibroblasts navigate two- and three-dimensional extracellular matrices, how this behavior is influenced by the architecture and mechanical properties of the matrix, and how migration is integrated with the other principal functions of fibroblasts, including matrix deposition, contraction, and degradation. New technologies and approaches should provide a better understanding of the molecular and cellular processes that drive fibroblast motility through intact tissue matrices. This insight into fibroblast physiology may lead to novel therapeutic approaches to control fibroblast migration and extracellular matrix deposition in wound healing and limit pathological fibrosis.

Matrix metalloproteinase-9 (MMP-9) regulates pathological remodeling processes that involve inflammation and fibrosis in cardiovascular disease. In their review, Yabluchanskiy and colleagues (6) summarize current understanding of MMP-9 physiology, including the effects of structure, regulation, activation, and downstream effects of increased MMP-9. By concentrating on the substrates of MMP-9 and their roles in cardiovascular disease, their laboratory explored the overall function and future direction of the translational potential of MMP-9-based therapies. Future successful in vivo studies using selective MMP-9 inhibitors may provide additional novel insights by which intervention of extracellular remodeling may lead to new approaches in treatment of atherosclerosis, hypertension, myocardial infarction, and heart failure.

Emphysema is a chronic, slowly progressing disease with no cure at the present time. In their review, Suki and colleagues (3) present a conceptual framework that illustrates how feedback mechanisms, including mechanical stresses, local extracellular matrix (ECM) stiffness, and stretch pattern, may interact with cellular signaling to produce molecules that can degrade lung tissue. Furthermore, they discuss the important role of mechanical stresses in both the pathogenesis and progressive nature of emphysema through lung remodeling as well as tissue destruction. Uncovering the cellular pathways of mechanotransduction may open new directions in emphysema research, with the possibility of discovering novel therapeutic targets. In addition, understanding mechanical stress-induced failure can have implications for quality of life, such as exercise tolerance and the type of exercise that does not elicit exacerbation, as well as improved mechanical ventilation of patients requiring ventilator support.

Just like the major organs of our bodies, subcellular organelles such as mitochondria, endoplasmic reticulum and lysosomes may become dysfunctional under conditions of stress. Organelle transfer is a novel physiological concept for intra- and intercellular signaling and regeneration. In their review, Rogers and Bhattacharya (2) describe the physiological mechanisms, subcellular structures, and conditions by which organelle transfer occurs. The review suggests that cell stress is a powerful stimulus for intercellular organelle transfer. Multipotent adult stem cells, mesenchymal stromal cells surrounding epithelial parenchyma in various organs, fibroblasts, and hematopoietic stem cells are most likely to be organelle donors. Focusing on these stem cells may provide a deeper understanding of this novel signaling process. Therapeutic implications of this research would be directed toward strategies that pharmacologically alter intercellular organelle transfer, either by augmenting it to replenish dysfunctional mitochondrial and lysosomes in the cell under stress or by blocking its occurrence in the spread of infection or the maintenance of malignant cells. Other areas for further exploration include the mechanisms that couple organelle transfer and nanotubes that cells use as conduits to transfer whole organelles between cells.

Autophagy, the lysosomal degradation pathway, is one of the most important links between the availability of extracellular nutrients and intracellular metabolism. In mammalian cells, autophagy is heavily dependent on the availability of growth factors, which are natural substances capable of stimulating cell growth and differentiation. In their review, Li and colleagues (1) focus on growth factor signaling pathways that are closely related to the induction of autophagy and discuss the critical roles of this cellular process in...
intracellular energy homeostasis, cell fate
determination, and pathophysiological
regulation. An understanding of the mo-
lecular mechanisms and functions of au-
tophagy induced by limited growth
factors may lead to therapeutic ap-
proaches for detection, treatment, and
control of diseases whose etiology in-
volves altered growth factor-related au-
tophagy—diseases as varied as spinal cord
injury, cancer, and diabetes.

No conflicts of interest, financial or otherwise,
are declared by the author(s).

References

1. Li TY, Lin SY, Lin SC. Mechanism and physiolog-
ical significance of growth factor-related au-
2. Rogers RS, Bhattacharya J. When cells become
3. Suki B, Sato S, Parameswaran H, Szabari MV,
Takahashi A, Bartolák-Suki E. Emphysema and
mechanical stress-induced lung remodeling.
4. Tschumperlin DJ. Fibroblasts and the ground
5. Vedula SRK, Ravasio A, Lim CT, Ladoux B. Col-
lective cell migration: a mechanistic perspective.
6. Yabluchanskiy A, Ma Y, Iyer RP, Hall ME, Lindsey
ML. Matrix metalloproteinase-9: many shades of
function in cardiovascular disease. Physiology 28:
391–403, 2013.