Introduction

Introduction to the thematic issue: Recognition of women leaders in Science

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Impact statement

It is with enormous pleasure that we seek, in this special thematic issue, to recognize some of the multitude of women leaders in the Biomedical Sciences. There is an ever-increasing number of women that are leaders in their scientific field, with fundamental roles in science, technology, engineering, and mathematics in all spheres of academia, medicine, industry, and public service. Women have made a major mark in their chosen fields and have helped raise the standards of excellence within them. Their timeless efforts have expanded our knowledge in a number of important areas and helped forge new pathways of discovery in the Biomedical Sciences leading to the development of new technologies and a better understanding of the underlying causes of a number of disorders.

Abstract

This thematic issue of Experimental Biology and Medicine is dedicated to the incredibly important contributions made by women leaders in the biomedical sciences throughout recent history. Scientists from many disciplines have contributed papers, both original research and state of the art reviews, to demonstrate the type of work being performed every day by women leaders committed to advancing scientific knowledge in their respective fields of specialization. In this introduction, we provide readers with a brief highlight of the information to be found in the invited papers.

Keywords: 3D-organoids, DENV vaccine, epilepsy, growth hormone secretagogue receptor, hemophilia, immunometabolism, lens development, stem cells

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We have invited contributions to this issue from women who are not only making a difference to their fields but are also strong mentors of young female scientists, since we believe that these women serve to inspire the next generation of women scientists. The contributors to this issue are from a cross-section of areas. They include both MDs and PhDs and many have invited female mentees to co-author their papers. Some of the authors are Directors of their units, belong to National Academies of Science, and/or are making impacts on public health policies. Other authors are at earlier stages of their career but are at the forefront of the state of the art and show clear engagement in the leadership of young researchers.

In the first article,[1] Janet Rubin and Maya Styner from the University of North Carolina provide a comprehensive analysis of how the skeleton is shaped by the physical environment. Particular emphasis is placed on how mechanical force can guide mesenchymal stem cell (MSC) fate. These mechanical forces are important at the level of the cell membrane where they can be translated into signaling pathways that can control gene expression in MSCs. This in turn can lead to cellular remodeling, rearrangement of cellular structure and reorganization of actin polymers between the cytoplasm and the nucleus. This reorganization can affect the balance of the MSCs in producing bone forming osteoblasts or energy storing adipocytes. This article emphasizes that mechanical forces, when applied to the skeleton, can modify the supply of phenotypically differentiated cells (i.e. osteoblasts and adipocytes), thereby altering skeletal mass and shape. Importantly, these findings may hold potential for improving cardiovascular and resistance exercise regimens that can protect against bone fragility and strengthen the skeleton during the loss of bone density and quality that is associated with aging.

Neuroscientist Iscia Lopes Cendes and colleagues from the University of Campinas, Brazil, present new studies on gene expression profiles in patients with sporadic and familial mesial temporal lobe epilepsy (MTLE). Professor Cendes' team previously described and defined a familial form of MTLE that is associated with hippocampal abnormalities.[2] They now provide evidence that, despite their phenotypic similarities, the familial and sporadic forms of this disease may possess differing underlying molecular mechanisms.[3] Based on the mRNA expression signatures in the tissue lesions of carefully diagnosed and characterized patients, the authors describe an elevated expression of biological pathways related to protein response, mRNA processing and synaptic plasticity in familial MTLE. The gene expression profile of the hippocampi from sporadic MTLE patients suggests a highly activated inflammatory response in these individuals. These mechanistic data could aid in the identification of candidate compounds that pave the way to the development of distinct therapeutic approaches for these forms of MTLE.

Yuxiang Sun from Texas A&M University and her collaborators have teamed up to provide a review on the expression and function of the growth hormone secretagogue receptor (GHS-R), which plays a primary role in the signaling of the orexigenic hormone, ghrelin.[4] GHS-R is expressed on the cell surface of immune cells, but its expression and function are modulated by the microenvironment. In particular, inflammatory conditions, such as the low-grade chronic inflammation that is associated with obesity, diabetes, and aging, often upregulate the cellular expression of GHS-R, where evidence indicates that this receptor contributes to both innate immunity and adaptive immunity. Ablation of GHS-R function on macrophages, for example, shifts cells from a pro-inflammatory to an anti-inflammatory phenotype. The authors emphasize that an understanding of modulation of GHS-R expression and GHS-R-mediated signaling in immune cells is essential for comprehending and defining the role and therapeutic applications of ghrelin signaling in immunity and in inflammatory diseases.

Camila dos Santos and her group at Cold Spring Harbor Laboratory study the epigenetic regulation of normal and malignant mammary gland development, particularly during pregnancy. They present an elegant review of three-dimensional (3D)-organoids and their use for studying breast cancer.[5] These multicellular, heterogeneous models are cultured from groups of cells isolated from mammary tissue to form mammary structures in culture. The review covers the history of breast tissue-in-a-dish, discusses optimal culture conditions, compares nondiseased and neoplastic breast systems, and looks at their applications. 3D-organoid systems may be extremely useful for high-throughput drug testing and have been instrumental in the study of both healthy and diseased mammary glands, providing mechanistic insight into breast cancer.

Cross talk between immune mechanisms and intracellular metabolic pathways is increasingly recognized. In their review,[6] Aisling Dunne and her colleagues from Trinity College, The University of Dublin, highlight damage-associated molecular patterns (DAMPs) as endogenous drivers of altered immune cell metabolism. Metabolic reprogramming of cells can occur as an adaptive response in an attempt to control the fate and function of cells. Like cancer cells and healthy proliferating cells that have long been known to display metabolic shifts, immune cells are also subject to metabolic pathway rewiring depending on their maturation and activation state, and in response to inflammatory stimuli. Activated cells have a higher energy demand and pro-inflammatory immune cell subsets, such as pro-inflammatory macrophages, often display upregulation of glycolysis, fatty acid synthesis, amino acid metabolism and the pentose phosphate pathway. On the other hand, naïve and immature cells and those associated with anti-inflammatory function present accelerated oxidative phosphorylation and fatty acid oxidation. Many inflammatory and autoimmune disorders display dysregulated immunometabolism and understanding the mechanisms of this reprogramming and its consequences opens up prospects for the identification of novel drug targets for treating these disorders.

Sue Menko and her group from Thomas Jefferson University provide new findings on the question of how resident immune cells migrate to the embryonic lens. Since both embedded vasculature and lymphatics are absent from the central light path in the embryonic eye, it is unclear how immune cells are recruited and populate the lens during development. The group shows, in this beautifully visual study, using immunofluorescence and high-resolution confocal microscopy of chicken embryo eyes, that ciliary zonule fibrils (fibrinillin-2) are the primary pathway for immune cells from the highly vascularized ciliary body to the avascular embryonic lens.[7] They found that the matrix proteins, fibronectin and tenascin-C, facilitate cell migration along the fibrinillin-2 zonule backbone. The findings presented expand the knowledge of how immune cell delivery to the lens can occur during its development and during responses to eye injury and pathogenesis.

Dengue is a mosquito-borne virus that has spread globally in recent decades with 5.2 million cases reported in just 2019. Dengue virus (DENV) infection has manifestations that range from an asymptomatic or mild presentation to the development of potentially fatal complications such as dengue shock syndrome. Four DENV serotypes (DENV1-4) exist that can all independently cause the broad spectrum of disease manifestations associated with DENV. Ana Fernandez-Sesma and her colleagues from Icahn School of Medicine at Mount Sinai, New York, from the National Institute of Allergy and Infectious Diseases (NIAID), NIH, Rockville and from Johns Hopkins, Rockville, characterize the innate immune inductions achieved by different formulations of the NIAID live attenuated tetravalent (LATV) dengue vaccine candidate.[8] This vaccine candidate is composed of variants of three DENV serotypes that are attenuated by a 30-nucleotide deletion (Δ30) and a fourth chimeric virus with the replacement of DENV-4 prM and E genes by DENV-2 genes on the rDEN4Δ30 backbone. The authors found that the rDEN-4Δ30 vaccine component was important to achieve a robust host innate immune response, which was characterized by an early and high secretion of IP-10 and IFNα2, and markers of dendritic cell activation and migration. Understanding the innate immune profiles of the different DENV vaccine strains is of importance for future vaccine design.

Hematologists Margareth Ozelo and Gabriela Yamaguti-Hayakawa from the University of Campinas, Brazil, provide a review on state-of-the-art gene therapy using adeno-associated virus (AAV) gene transfer for hemophilia,[9] where the first gene therapy product has recently been licensed for use in the European Union for treating severe hemophilia. The authors discuss issues of gene therapy safety, efficacy, and durability. They also look at how monitoring of therapy response could employ strategies that go further than looking at coagulation factor activity, such as determining the duration of coagulation factor expression and observing musculoskeletal health and chronic pain. One setback that can occur in AAV-based gene transfer is vector-directed immunogenicity. The authors discuss how both innate and adaptive immune responses may contribute to this phenomenon, where mitigation of the immune response may be one approach to improving the success of this life-changing treatment.

In summary, while fully acknowledging the inclusion of just a tiny sample of the women who are leading biomedical science in this Thematic Issue, we would like to celebrate the achievements and contributions of these and all women who have been helping to develop our next generation of scientific researchers. All have managed to carve a niche for themselves and their mentees in their fields of interest, generating high-impact research that has been making a difference to basic, translational, and clinical biomedicine. Congratulations to all this issue's authors and their colleagues who so enthusiastically contributed to this collection of articles!

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