

Synapses are the sites of communication between neurons and their formation is mediated by a wide variety of genes encoding synaptogenic proteins (e.g. neuroligins, neuroligins, cadherins, ephs/ephrins, integrins, etc.). One of the protein families that is implicated in synapse wiring but poorly understood is the immunoglobulin superfamily (IgSF). Cameron and McAllister highlight the critical role of IgSF molecules in synapse formation particularly in the context of vertebrate brain. The authors anticipate that deducing the IgSF code for synapse formation may eventually lead to novel treatments for psychiatric disorders caused by defected IgSF-induced synapse wiring.

Reviews describing various aspects of chromosome structure function and dynamics are well compiled in this volume. Lange provides an elaborate review on current knowledge of shelterin-mediated telomere protection and highlights differences between human and mouse shelterin. Shelterin structure, DNA binding features and shelterin accessory factors are comprehensively addressed in this article. Seeber *et al.* discuss critical regulators of chromatin mobility in response to DNA damage. This review suggests that centromeric tethering, telomeric tethering, microtubules and actin filament influence chromatin mobility.

One of the major challenges in biomedical research is to understand the interface between the ageing process and the manifestation of age-associated diseases. Although different research activities are currently being conducted to understand the process of ageing<sup>4</sup>, there is no unifying concept that explains better the complex biology of ageing. Two review articles especially focus on this issue. Mertens *et al.* emphasize the key features of ageing that appear to drive neurodegeneration and age-associated diseases. They discuss the extent to which induced pluripotent stem cells reflect aged neurons.

As a whole this is a highly informative volume that consists of various high quality articles on key issues in genetics. Molecular biologists will find a number of articles in this volume extremely interesting as promised by its earlier volumes. This volume provides major research findings in contemporary topics and opens up new research avenues towards understanding some long standing questions from different sub-fields of genetics.

1. Lind, M. I. *et al.*, *Heredity*, 2018, **121**, 205–209.
2. Diaz, M. and Pecinka, A., *Genes*, 2018, **9**, 36.
3. Brochier-Armanet, C. *et al.*, *Nat. Rev. Microbiol.*, 2008, **6**, 245–252.
4. López-Otin, C. *et al.*, *Cell*, 2013, **153**, 1194–1217.

G. SUBRAHMANYAM\*  
M. CHUTIA  
K. P. ARUNKUMAR

*Central Muga Eri Research and Training Institute,  
Central Silk Board,  
Ministry of Textiles, Govt of India,  
Lahdoigarh,  
Jorhat 785 700, India  
\*e-mail: subbugangavarapu@gmail.com*

#### **Annual Review of Physiology, 2019.**

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This volume of *Annual Review of Physiology* starts with two articles on the fate and function of mitochondria. The first article on the ‘Evolving concepts of mitochondrial dynamics’ focuses on the issues of mitochondrial fusion, mitochondrial fission, trafficking pathways and mitophagy. The article brings into focus mitochondrial dynamics in the heart which is the most energy-dependent and mitochondrial-rich mammalian organ (accounting for a third of the weight of cardiomyocytes). While the article is primarily physiological, the authors draw attention to the possible role of mitochondrial function in the genesis of cardiac hypertrophy which is not an uncommon clinical condition. The second article on the ‘Maintenance of skeletal muscle mitochondria in health, exercise, and ageing’ addresses a significant health issue at a population level. The ageing population in all countries of the world is steadily increasing and one of the issues of increased longevity is sarcopenia or the loss of skeletal muscle mass, with all its attendant sequelae. In young populations physical inactivity affects skeletal muscle quality. The authors provide compelling cellular evidence for the positive role of exercise in mitochondrial biogenesis and the maintenance of muscle mass, and the case for

providing exercise as a non-pharmaceutical method to enhance mitochondrial function in ageing and muscle disease. These studies are particularly important because they add valuable support and enhance the physiological understanding of the large number of physical activity interventions already completed and underway. This article resonates with the very last article of the book which focuses on the ‘Physiology of optimising health with a focus on exercise as medicine’. The article has a telling quotation of Sir Edward Stanley – ‘those who think they have not time for bodily exercise will sooner or later have to find time for illness’. This article has particular relevance in India where the prevalence of physical inactivity is particularly high and where chronic non-communicable diseases such as diabetes, hypertension, and coronary heart disease, among a host of other illnesses are increasing. Exercise is protective against these diseases and this has been shown in a variety of epidemiological study designs including observational cross-sectional studies, cohort studies and intervention studies. While the article reviews much of the public health data, it also focuses on the physiological basis of these physical inactivity–disease relationships by exploring the link between low physical fitness, abdominal adiposity and inflammation, muscle as an endocrine organ and the anti-inflammatory actions of myokines. The article is timely but also underscores the large relatively unexplored area of the physiology of physical inactivity and sedentary behaviour. While to most people it is intuitive that if exercise protects against disease, sedentary behaviour must be bad, there is only now an emerging body of data which explores the specific physiological sequelae during sustained physical inactivity such as prolonged sitting, immobilization, bed rest, etc. This is an area which I hope will be covered in future editions of the *Annual Review of Physiology*.

The maternal changes that occur during pregnancy has been the subject of considerable investigation for reproductive physiologists. The rapidly growing foetus demands an adequate blood supply in the pregnant women. This is achieved through an expansion in plasma volume, an increase in cardiac output, a reduction in peripheral resistance and an increased uteroplacental blood flow of the order of 10 to 20 times. Uteroplacental

insufficiency which disrupts the supply of nutrients and oxygen is important clinically because it is associated with intra-uterine growth retardation and low birth weight. Low birth weight is a significant issue in India. The article 'Plasticity of the maternal vasculature during pregnancy' provides an overview of the maternal circulation during pregnancy with a specific focus on the endothelial and vascular smooth muscle plasticity. This area is important because there may be epigenetic changes that modulate the process of maternal cardiovascular adaptation. In India, in many areas, pregnant women are exposed to high levels of indoor air pollution due to the use of fossil fuels during cooking in poorly ventilated homes. Exposure to certain particulates increases vascular reactivity and it would be interesting in an Indian context to determine whether plasticity of the maternal utero-placental circulation is affected by indoor air pollutants.

Chronic visceral pain, i.e. pain that originates from the organs affects more than a fifth of the global population. This pain is typically diffuse and poorly localized and may involve more than a single organ. Apart from the primary pathology, chronic visceral pain is associated with higher levels of anxiety and depression. This, therefore, is of considerable importance to a clinician. In the article 'Visceral pain' the authors review the mechanisms that are associated with inflammatory and functional (non-inflammatory disorders also associated with visceral pain) bowel and bladder disease. They highlight the visceral pain pathways and the role of various factors including an altered gut microbiome, mucosal permeability, immune responses and stress in the pathogenesis of visceral pain. A better understanding of these mechanisms is important in order to develop appropriate treatment strategies since conventional analgesics are not only less efficacious but may also exacerbate underlying disease. Another article which will appeal to practising clinicians is 'Biomarkers of acute and chronic kidney disease'. For close to a century, serum creatinine has served as the screening test for renal function despite its limitations including the fact that it might detect kidney injury at a later stage. Serum creatinine also largely reflects glomerular function which is focused on filtration. However, renal function also includes reabsorption of

substances and secretion and these tubular functions which occur at various points in the nephron are not adequately reflected by changes in serum creatinine. Indeed, serum creatinine may be unchanged in the presence of significant tubular injury. There is thus a need to evaluate more specific biomarkers of renal function that reflect injury (including the site of injury along the nephron), tubular function and renal inflammation. This is the subject of the article. Written lucidly, the article is easy to read and the authors summarize various biomarkers that fulfil clinical needs in areas of diagnosis, prognosis (risk of outcomes) and for predictive purposes (response to interventions).

Humans have started moving to high altitudes for a variety of reasons – adventure sports including mountaineering and trekking and the need to maintain army personnel at high altitude border outposts. For many generations, however, humans have also moved to high altitudes to live and sustain their livelihoods – these groups are referred to as native highlanders and they exist across continents. They include, for instance, the Andean natives, Ethiopian highlanders and Tibetans and Sherpas who live at high altitudes in the Himalayas and the Tibetan plateau. Physiologists have used this natural experiment to study adaptation to high latitude by comparing native highlanders to dwellers at sea level and those who travel from low to high altitude and experience acclimatization. The article 'Evolved mechanisms of aerobic performance and hypoxia resistance in high-altitude natives' attempts to shed new light on the mechanism by which species adapt to the hypoxic conditions of high altitude using the method of comparison of dwellers at various altitudes as also comparative physiology studies of mammalian and non-mammalian high-altitude species. The focus of the article is on understanding the oxygen transport cascade from the point of acquisition of oxygen in the lungs to the utilization of oxygen for metabolism in the tissues under conditions of rest and during exercise. Also included in the article is a discussion of how high-altitude natives attenuate the maladaptive responses to chronic hypoxia including hypoxic pulmonary hypertension which would precipitate right heart failure, sustained erythropoiesis which would increase blood viscosity

and cardiac work, and enhanced sympathetic nervous activation via the hypoxic chemoreflex. Although the article provides many new details, the authors list several important areas related to the capacity for phenotypic plasticity, substrate utilization during exercise and changes in the skeletal muscle phenotype that explain substrate use in high-altitude natives as areas that still need to be explored and this highlights the large number of unresolved physiological questions in this area.

Thermoregulation refers to the maintenance of core body temperature in the face of either an increase or decrease in temperature. 'Central mechanisms for thermoregulation' reviews the central neural networks involved in thermoregulation in term of the anatomy, neurotransmitters involved and functional inter-relationships of the elements of the network. Classical lesioning and stimulation studies evolved the view of a heat loss and heat maintenance centre in the hypothalamus. Current understandings have extended that model. What I found particularly interesting was the relatively brief discussions on the preoptic mechanism that triggers fever during infection and the central circuits involved for behavioural thermoregulation.

The above topics are a sample of what is contained in the annual review. As always, the Annual Review is divided into subsections largely on the basis of the biological systems in the body. The special topic of the review is devoted to Angiogenesis and Lymphangiogenesis. Both of these areas are discussed in terms of the growth of tumours, among others.

I found this edition of the *Annual Review of Physiology* an interesting mix of articles which catered to the needs of clinical/medical and cellular physiologists. A strength of many of the articles is that they provided a succinct summary of the article and a section on 'future directions'. These I think are invaluable for a scholar who is intent on reading across subject areas as opposed to the focused researcher delving into a specific area. The Annual Review continues to live up to its reputation for thoughtful and topical articles that appeal to a wide audience.

MARIO VAZ

*Department of Physiology,  
St John's Medical College,  
Bengaluru 560 034, India  
e-mail: mariovaz@sjri.res.in*