

## The diversity of retinoid biology

Retinoids comprise both naturally occurring and synthetic molecules that have a structural resemblance to all-*trans*-retinol, which by definition is vitamin A. Thus, the term retinoid is used to refer both to vitamin A and its metabolites and to chemically-related compounds that have been specifically synthesized as potential pharmacological agents for treating disease. It has long been known that the naturally occurring retinoids are required for maintaining immunity, barrier function, male and female reproduction, embryonic development, cognitive function, and vision. Over the last decade it has become increasingly clear that aberrant actions of naturally occurring retinoids and retinoid-related proteins are associated with development of metabolic disease, including obesity, type II diabetes, liver disease and cardiovascular disease. At the cellular level, retinoids are needed for maintaining normal cell proliferation, differentiation and apoptosis. Consequently, for over 50 years there has been much research interest focused on the use of both natural and synthetic retinoids in the treatment of proliferative disorders, especially cancers and skin disease.

The diversity of the biological actions of retinoids will be showcased in a Focused Issue of *HepatoBiliary Surgery and Nutrition (HBSN)* focused on these compounds. This Focused Issue will be published in two installments and will consist primarily of review articles that summarize some aspect of retinoid physiology or action, although two research articles are also included.

The first issue provides three review articles and one primary research article. The first review summarizes findings on the clinical use of a synthetic retinoid to block hepatocellular carcinoma development and progression in patients. This article provides insight into the pharmacological use of retinoids for treating hepatocellular carcinoma and points to future research that needs to be undertaken in this area. The second review considers at the molecular level the role of stimulated by retinoic acid 6 (STRA6) in regulating cellular retinol uptake and efflux. STRA6 was first described in the literature as a cell surface receptor for retinol-binding protein, the sole specific transport protein for vitamin A in the blood. More recent studies have established a role for STRA6 in mediating cellular efflux of retinol. Moreover, STRA6 has attracted considerable research attention due to its association with both genetic and other diseases. This is followed by a third review that provides a very comprehensive consideration of retinoid-xenobiotic interactions. This research area is in our view underappreciated. The diverse literature in this area is convincing, both that retinoids play key roles in modulating the metabolism and toxic actions of xenobiotics, and that xenobiotic exposure adversely affects retinoid metabolism and physiologic actions. Finally, the last article of the first installment of the *HBSN's* Focused Issue on retinoids, reports very exciting new findings showing that *in utero* exposure to alcohol (ethanol) perturbs retinoid homeostasis in adult rats. If this finding can be extended to humans, this would have a considerable impact for understanding alcoholic disease.

The second installment of *HBSN's* Focused Issue on retinoids will be published later this year and will consist of two reviews and one research publication. The first review is focused on the actions of retinoids in the adult pancreas. Retinoids have important roles in maintaining the normal endocrine functions of both  $\alpha$ - and  $\beta$ -cells in the islets of Langerhans. Retinoids have been shown to be needed for maintaining both glucagon and insulin secretion. Independent of retinoid actions in the endocrine pancreas, pancreatic stellate cells are thought to contain large quantities of retinoid. When these cells become activated leading to pancreatic fibrosis and later stage pancreatic disease, pancreatic stellate cell retinoid stores are lost and aberrant expression of a number of retinoid-associated parameters is observed. Next, novel findings that show a direct role for retinol in mitochondrial respiration will be reviewed. Based on this published data, the second review proposes a novel scheme for understanding a retinol-dependent process that is important for cellular energy generation. The author provocatively proposes that retinol can act as an electron acceptor in the mitochondrial respiratory chain. Importantly, this is another example of a retinoid action that does not involve the retinoid nuclear receptors. The final article of this Focused Issue is a primary research report that provides findings from liquid chromatography tandem mass spectrometry (LC/MS/MS) studies aimed at establishing all-*trans*-retinoic acid levels in a number of human and animal tissues and isolated cells. Since all-*trans*-retinoic acid is both chemically and biologically labile and since it is present at only very low levels within tissues and cells, it is important to apply recent advances in analytical instrumentation to gain better understanding of all-*trans*-retinoic acid metabolism and actions within cells and tissues. The final research article achieves this goal.

We would like to thank all of the authors who have provided excellent reviews and primary research contributions to this Focused Issue. We believe that the time and care that the authors have invested in their contributions to this *HBSN's* Focused Issue renders this Focused Issue both novel and exceeding informative.



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