EDITORIAL

Lipids in Cancer Cell Biology and Therapy

Cancer-related morbidity is one of the leading causes of deaths in the world. Due to the social and health impact of cancer, research on cellular and molecular pathways leading to oncogenesis and carcinogenesis is one of the most active areas of biomedical investigation. Moreover, the uncovering of pathways that foster cancer growth and cell death resistance may also result in the development of more efficient therapeutic options for the treatment of cancer. In this special issue of Anti Cancer Agents in Medicinal Chemistry, a group of expert leaders summarize emerging evidence on the exciting role of cholesterol and sphingolipids (SLs) in the regulation of cancer cell biology and therapy. In addition to playing a key structural role in biological membranes, recent data have uncovered a critical function for cholesterol and SLs in the modulation of essential pathways involved in cancer cell biology. Particularly, ceramide and cholesterol regulate cell death pathways and hence play a crucial role in determining the susceptibility of cancer cells to current therapy, thus providing a rationale for novel therapeutic combinations.

In this regard, Ballereau *et al*., examine the role of ceramide functionalization at the C1-OH position as a promising approach for cancer therapy (1). Although ceramide is well recognized as a proapoptotic lipid moiety, ceramide metabolism in cancer cells is altered giving rise to other metabolites involved in tumor progression and drug resistance. The authors review data indicating the key role of enzymes that modify ceramide at the C1-OH position generating other biologically important SLs in cancer, such as sphingomyelin, ceramide-1-phosphate or glucosylceramide. Thus, modulating these enzymes may open novel opportunities for improving current chemotherapy.

In the review by Mullen and Obeid, the authors provide an extensive overview of the role of ceramide and apoptosis (2). In particular, the authors explore enigmatic connections between sphingolipid metabolism and programmed cell death, particularly focussing on the role of de novo sphingolipid synthesis and sphingosine salvage in producing proapoptotic ceramide, involving mitochondrial membrane permeabilization. Due to the critical role of mitochondria in the regulation of cell death pathways this connection may be of relevance in regulating cancer cells susceptibility to apoptosis and chemotherapy.

Along these lines, Delgado *et al.*, (3), summarize SLs metabolism and provide evidence for the role of sphingolipid analogs as metabolic modulators in cancer cell therapy. Of significance for solid tumors like renal carcinomal and liver cancer, the authors present data exploring the role of sorafenib with sphingosine kinase inhibitors to modulate cancer cell death susceptibility and the development of novel small molecule inhibitors of SLs metabolism to potentiate current therapy.

In addition to the role of ceramide in apoptosis regulation, this lipid can also serve as a precursor for complex glycosphingolipids, including gangliosides. Sorice *et al.*, review the role of ganglioside GD3 in cell death regulation (4). They provide compelling evidence linking the trafficking of GD3 to mitochondrial membranes to regulate the susceptibility of cells to Fas-mediated apoptosis. Intriguingly, GD3, by interacting with mitochondrial raft-like microdomains, may trigger specific events involved in the apoptogenic program, introducing an additional task for identifying new molecular targets of anti-cancer agents.

As a key component of biological bilayers, cholesterol has emerged as a modulator of cell death pathways with a potential role in cancer cell therapy. In this respect, Lucken-Ardjomande (5) presents current evidence about the role of cholesterol in modulating mitochondria membrane permeabilization. In this novel function, cholesterol regulates mitochondrial membrane physical properties determining the ability of proapoptotic Bcl-2 family members to permeabilize mitochondria and engage the apoptosome.

As one of the leading causes of cancer-related deaths, Morales *et al.,* (6) review the role of cholesterol and ceramide in hepatocellular carcinoma. The authors focus on the emerging role of mitochondrial cholesterol in determining the susceptibility of hepatocellular carcinoma to chemotherapy, opening the possibility for designing novel targets for treatment and the rationale for proposing combined therapies with current agents and inhibitors/modulators of cholesterol and ceramide metabolism.

Finally, related to the role of cholesterol in cancer, Garcia-Ruiz *et al.,* (7) explore the effects of statins and protein prenylation in cancer cell biology and therapy. Targeting the heart of the mevalonate pathway, statins not only reduce the synthesis of cholesterol but blunt the synthesis of isoprenoids and hence alter protein-prenylation, a critical event in the posttranslational modulation of proteins involved in the regulation of cell cycle progression, proliferation and signaling pathways, including the Hedgehog pathway. Current trials indicate a potential beneficial role of statins in different solid tumors, including colorectal, pancreatic and liver cancer. However, the potential of combined therapy with statins and currently used chemotherapeutic agents in these prevalent cancer types needs to be further explored.

We hope this collection of timely reviews may spark the interest in this field of oncology and promote more basic research to understand the role of cholesterol/ceramide in cancer cell biology to exploit their potential as novel anticancer strategies.

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