The Novel Use of Lipids as Diagnostic Tools and Therapeutics in Cancer: Recent Insights and Challenges

Regardless of manifold scientific and medical advances, cancer remains a leading cause of death globally. Current developments in diagnosis and treatment modalities have significantly increased the overall survival and quality of life in cancer patients. Alterations and/or abnormality in biological parameters in the extracellular and intracellular environment modulate tumorigenic activity at the primary tumor and metastatic sites. An abundance of research articles has linked the dysregulation of intrinsic lipid molecules and their metabolites with cancer growth, metastasis, and therapy resistance in varied experimental models and clinical studies. This thematic issue has emphasized the work focused on lipid homeostasis, lipid metabolism, re-programming of lipid metabolic networks, lipid metabolites, and phospholipids linked with tumorigenic potential and drug resistance, along with metastatic activity. This issue aims to provide information concerning the involvement of obesity, dietary habits, and other factors, such as mitochondria, in lipid-linked cancers. Additionally, this thematic issue targets developments in identification of fatty acids, which can be used in the treatment of cancers and treatment-associated complications as well as novel approaches in drug delivery. Eight articles have been included to describe the above mentioned thematic issue.

Abalo R’s research group has underlined the dysregulation of various lipid molecules including cholesterol, LDL-cholesterol, HDL-cholesterol, saturated and unsaturated fatty acids, and triacyl glycerides (TG) in cancer patients [1]. Similarly, various polar lipids, glycercophospholipids, sphingophospholipids, poliketides are also often dysregulated in cancers, and this dysregulation is also linked with patient survival. This study has summarized the important research works focused on lipidomics as a tool to identify new biomarkers, but lipidomics still lacks a gold standard. It would be necessary to go deeper into the associations between the candidate biomarkers and the outcomes, considering the possible confounders, to clarify the pathways where these candidates are involved, and to elucidate if the candidates are biomarkers of cancer. In continuation, Rao CV’s research team has further pointed out that the dysregulation of TG level and regulatory genes especially involved in its metabolism may hold promising drug targets for colorectal cancer therapeutics [2]. Through literature survey and cancer database analysis, this study has pointed out a few crucial target genes (e.g., HMGCoA reductase and Fatty acid synthase), but in-depth analysis also brings a few additional TG mediator genes (e.g., ATGL, MAGL, GPAT2, and FABPs) as cancer biomarkers and promising drug targets. Thus, dietary interventions and pharmacological inhibitors together could prevent cancer progression and metastasis associated with the dysregulation of lipid metabolism. Kaur M’s research team has highlighted the role of cellular cholesterol in cancer drug resistance [3]. Indeed, their analyses found various microRNAs which regulate breast cancer stem cells, cholesterol biosynthesis and breast cancer drug resistance. For instance, hsa-miR-34a-5p and hsa-miR-373-3p directly target breast cancer stem cell markers, CD44 and CD24, and INSIG2. The authors propose that microRNAs that target breast cancer stem cells and cholesterol genes could be possible therapeutic targets, in an effort to eliminate breast cancer drug resistance. Majehrzak, K et al., have underscored the influence of A-FABP (Fatty acid binding protein A) in obesity-associated cancers [4]. In fact, adipose tissues and cancer associated adipocytes not only supply fuels (fatty acids) to cancer cells but also provide various factors, including hormones, cytokines, adipokines (leptin and adiponectin), which favor tumor progression at primary and metastatic sites. This article has noted crucial genes/signaling (e.g., IL6-STAT3-ALDH1, PI3K-AKT, ROS and DNMT1) which are modulated by A-FABP; moreover, adipocyte master regulator PPAR may also control the A-FABP level. Thus, targeting A-FABP could be a therapeutic strategy for the treatment of obesity-associated cancer patients. Kumar A’s research group has demonstrated a key role of various bioactive lipid molecules, including sphingosine-1-phosphate (S1P) and lysophosphatidic acid (LPA), which regulate several tumorigenic activities, including cell proliferation, survival, migration, angiogenesis, invasion, and response to chemotherapeutic and immunotherapeutic drugs [5]. Both S1P and LPA signaling pathways regulate homing of tumor-infiltrating immune cells in the tumor microenvironment. In fact, immune checkpoint inhibitor anti-PD1 in combination with a sphingosine kinase inhibitor showed enhanced efficacy in tumor killing effect of anti-PD1 in various animal model studies, and thus, propose them as co-therapeutics along with immunotherapy towards better patient response as well as improved overall survival in cancer patients. Sharma L’s research team has focused on the importance of metabolic reprogramming in mitochondrial respiration and lipid metabolism, and the interplay between lipid metabolism (fatty acid synthesis and fatty acid oxidation) and mitochondria in cancer initiation, progression and metastasis [6]. They have highlighted that the therapeutic drug candidates which target de-novo lipid biosynthesis and fatty acid oxidation along with mitochondrial pathways are to be further explored together in modulating the metabolic reprogramming for enhancement of cancer therapeutic efficacy.

Mandal CC’s research group has given an insight on non-toxic omega 3 fatty acids as therapeutic partners for treating cancer patients [7]. Still, conventional cancer treatments often pose a threat, such as off-target toxicities, tumor relapse, metastasis and drug resistance. Studies conducted at epidemiological, in vitro, in vivo and clinical levels have suggested that omega-3 fatty acid as a combination partner with other therapeutic drugs that exhibit not only anti-cancer potential but is also beneficial for cancer patients. Thus, omega-3 fatty acid, along with conventional therapies, has been shown to overcome the complexities
of cancer such as metastasis, drug mediated off-target toxicity, tumor relapse and drug resistance. Omega-3 fatty acid majorly contributes as a partner by targeting various key players, including NFκB, ROS and inflammatory cytokines that increase the effectiveness of therapies with the least chances of tumor recurrence. Raza K’s research team has focused on the possibility of the use of lipid molecules as nanocarriers for effective drug delivery [8]. Lipid-based nanocarriers could be the best option to nanoencapsulate the poorly soluble and permeable taxanes for cancer treatment, since these systems have various capacities, including enhancement in bioavailability, delivery and efficacy of drug molecules, and reduction in dosing frequency and efflux mechanism. The taxanes *i.e.*, paclitaxel and docetaxel are most potential, but the therapy often exhibits various side effects. However, the lipid-based nanoformulation of these taxanes may be clinically more effective, cost-effective and stable, and it may have fewer side effects.

Though this brief issue may not cover all the current relevant research works, this issue could be beneficial for readers and scholars focused on lipid metabolism and cancer.

REFERENCES


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