USING LIPIDOMIC PROFILING TO IDENTIFY NOVEL CANCER BIOMARKERS

Lipidomics is defined as the large-scale profiling and analysis of lipid expression in cells using analytical chemistry and is applied similarly to other types of "-omics" analyses. Lipids are widely expressed in all tissues and involved in multiple cellular processes including metabolism, cellular signaling and membrane formation. Lipid profiling has expanded to include multiple types of lipids such as fatty acyls, glycerophospholipids, sphingolipids, cholesterols, prenol lipids and polyketides[1] using several techniques that are typically based on mass spectrometry (MS). Given the key roles that lipids play in cellular physiology, it is not surprising that lipid profiles have been reported to be dysregulated in many disease areas including cardiovascular disease[2] and various cancers[3, 4].

Lipid expression is dysregulated in cancers to support several cellular processes. The metabolism in cancer cells tends to be higher than normal cells to support rapid growth and proliferation, so cancer cells have been shown to have higher rates of lipid (including cholesterol) synthesis and lipid oxidation[5]. Due to rapid cell proliferation and growth, tumors require higher levels of lipids for membrane formation and cellular signaling that, in turn, increases expression of enzymes involved in lipid synthesis. Along with lipidomic profiling, there is active research in evaluating altered expression of enzymes and cofactors associated with lipid synthesis as cancer biomarkers. Cancer cells have been shown to have different lipid composition in the cell membrane suggesting that lipid remodeling could be another hallmark of tumors[1]. Dysregulated lipid profiles also impact the tumor microenvironment (TME) by affecting the expression of cytokines and other soluble factors as well as altering immune cell structure and function[1]. Tumor derived cytokines induce lipid accumulation resulting in the activation of immunosuppressive mechanisms[5]. Additionally, changes in lipid metabolism have been reported to impact macrophage polarization and function. M1 or normal macrophages typically have higher levels of fatty acid synthesis while M2 or tumor associated macrophages tend to have higher levels of lipid oxidation to supply energy to rapidly proliferation tumor cells[6].

Lipidomic profiling is increasingly being performed using a method call "shotgun lipidomics"[1]. In this approach, most of the major and minor lipids in a tissue sample can be directly profiled using mass spectrometry without the need for chromatography-based purification. The shotgun approach is fast and sensitive and requires less sample which can be critical when working with limited samples from human patients. The combination of improved mass spectrometry methods and increasing knowledge of the importance of dysregulated lipid metabolism in cancers has resulted in the recent publications of a couple of very interesting papers[3,4]. One publication used a 5-lipid panel (phosphatidylcholine, diacylglycerol, sphingomyelin, phosphatidylinositol and a glycosphingolipid HexCer-AP) to differentiate between squamous cell carcinoma and adjacent normal tissues[3]. This study is particularly interesting as a defined panel is easier to use and analyze, especially in a clinical setting, compared to a large lipidomic data set. However, follow up studies need to be performed to characterize the lipid panel for sensitivity and specificity and more importantly, correlate the data with clinical prognosis and outcome. Another publication reported the use of lipidomic profiling in pancreatic ductal adenocarcinomas (PDAC)4. PDACs are difficult to diagnose and in most cases, the disease has progressed to later stages where treatment options are limited. Therefore, there is a lot of clinical interest in a noninvasive screening method to detect early stage PDAC. A research group in the Czech Republic led the study that analyzed over 800 PDAC samples to identify reproducible changes in lipid profiles. Interestingly, the lipid profiling method showed greater accuracy than the established CA 19-9 blood test that is used to diagnose PDACs and other solid tumors[4]. The lipidomic profiling method showed highest sensitivity and specificity in combination with the CA19-9 test suggesting that both tests can be performed from blood samples to diagnose PDAC at an early stage.

Based on the exciting data from squamous cell carcinomas and PDACs, it is very likely that other types of tumor indications will be evaluated using lipidomic profiling. Though this type of profiling has not been vetted in a clinical setting, it is very likely that additional studies will pave the way for lipid profiling, either as a panel or as a complete -omics data set, to be used as a robust diagnosis tool for several tumors.

References:

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