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Peeking inside the sphingolipid network in lung cancer

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Lung cancer is the leading cause of cancer-related mortality worldwide, with a 5-year survival rate of 4–17%, depending on the stage and genetic factors [1]. Lung cancer is often asymptomatic, and when detected and diagnosticated, it is frequently metastatic. Early detection screening becomes critical for the treatment's success, which typically includes radiography and low-dose computed tomography (CT), being the last more efficient, but with a concerningly high number of false positives [2]. Liquid biopsies are non-invasive, and they are helpful to monitor tumor progression and treatment response. However, lung cancer lacks early diagnostic biomarkers with high sensitivity and specificity.

The expansion of lipidomics techniques has revealed sphingolipids as master regulators in cell signaling in many diseases, including lung cancer. Sphingolipids are a class of lipids, originally thought to be only structural components in biological membranes. However, for the last 30 years, a growing number of signaling pathways have been shown to be tightly regulated by different sphingolipid species. Many of these sphingolipid-driven pathways involve biologies with high significance in cancer progressions such as cell proliferation, several forms of cell death, cell differentiation, angiogenesis, and cell migration [3]. However, many of the putative effector proteins directly responding to sphingolipids have not been clearly proved to interact with these sphingolipids (with the exception of sphingosine-1-phosphate [S1P] and the five identified S1P-receptors). Thus, although we could list the few hundred sphingolipid species in one column and the effector proteins and biologies in another column, it would not be possible to draw clear connecting lines between the two columns. This is partly due to the complexity and still poor knowledge of the sphingolipid network. Sphingolipids comprehend a few hundred species, forming an interconnected metabolic tree, where the regulation of one species is tightly related to the other species [4]. Therefore, it is very challenging to identify a single species responsible for a specific biology. Moreover, one single species of sphingolipid measured at the cellular level is the resulting sum of many different subcellular pools, each one with a potentially different function and regulated by a battery of genes resident in a subcellular compartment, with the same enzymatic activities as found in other compartments, but with a completely different regulation [5]. Besides sphingolipids acting as a second messenger, their global dynamic composition in biological membranes has been shown to define that membrane's biophysical properties. Perturbations of this composition in response to homeostasis but also in response to disease have been related to activating specific signaling pathways [6]. These points might generate confusion when trying to translate the cellular mechanisms involving sphingolipids and their metabolizing enzymes to the complexity of the tumor tissue.

In this article in EBioMedicine, Ping-Pui Wong and colleagues [7] reported two lipid species in serum as specific biomarkers in lung cancer. In their work, they analyzed the expression level of 31 enzymes from the sphingolipid network across several gene-expression databases, finding 50% of the enzymes were consistently dysregulated. The mRNA expression of two of these genes, B3GNT5 and GAL3ST1, showed a strong negative correlation in tumor tissue compared to normal tissue. This dysregulation on mRNA expression was also correlated with the prognosis of the patients. Interestingly, the enzymatic products of these genes, sulfatides and lacto-/neolacto series of glycosphingolipids, were found to be altered in the patient serum. The authors showed that these lipids' serum levels predicted lung cancer at an early stage, and they proposed them as novel biomarkers for lung cancer.

Understanding the biological relevance of sphingolipid diversity [8] and why there are so many sphingolipid-related diseases represents a challenge. An important message from this work is that disease-driven perturbations on sphingolipids do not result from the dysregulation of individual genes but from tuning the whole sphingolipid network. This is evidenced by building a network of sphingolipid correlations (positive and negative correlations) and drawing the network where all sphingolipid species are simultaneously coregulated, which, when plotted it takes the shape of a circular network [7,9].

This work highlights the level of integration of the sphingolipid pathway, metabolic networks, and lung cancer progression. However, similar sphingolipid co-regulation can be suspected in neural development, several types of cancer, and other diseases [10]. Future work should attempt to 'hack' the topology of the correlated network of sphingolipids, including gangliosides, and solve the 'enigma' of the

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sphingolipid code: from the sphingolipid composition to disease, cellular biology, and signaling pathway.

Declaration of Competing Interests

The author declares no conflict of interest

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