The ion channel and transporters gene expression profile indicates a shift in excitability and metabolisms during malignant progression of Follicular Lymphoma

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The purpose of the present study is to define a specific gene expression profile (GEP) of Follicular Lymphoma (FL), and compare it with that of the more aggressive Diffuse Large B Cell Lymphoma (DLBCL), focusing on the expression profile of those genes encoding for "ion channels and transporters" (ICT), using microarray technology.
cDNA microarray data were collected both from patients enrolled for this study, and from public datasets. In FL the ICT-GEP showed a substantial down regulation of calcium channels' encoding genes, while were overesxpressed both the K+ channel encoding gene *KCNN4*, which encodes for KCa3.1 involved in the Ca signalling in B cells and *SLC2A1*, which encode the Glut1 glucose transporter. *SLC2A1* turned out to represent the hub of a functional network, connecting channels and transporters in FL and is the hallmark of the main metabolic characteristics of cancers, i.e. aerobic glycolysis, stressing the relevance of the Warburg effect in FL.
Relapsed FL patients were characterised by 38 differentially expressed ICT genes, among which *ATP9A*, *SLC2A1* and *KCNN4* were under expressed. The down regulation of *KCNN4*, and hence of Ca^{2+}-dependent K+ currents indicates less excitability of FL cells[1], while the down regulation of both Glut1 and the creatine transporter suggests a metabolic shift far from the Warburg effect, leading to down regulation of glycolysis. This shift is also confirmed by the fact that one of the most up regulated genes is *ATPAF2*, one of the factors involved in mitochondrial functioning[2]. Furthermore, deregulated glycolysis and fatty acid metabolism has been linked with chemoresistance in multiple cancer types[3].
The same procedure applied to DLBCL, led to the identification of a completely different profile of K^+ channel encoding genes, and an over-expression of the fatty acid transporter-encoding gene *SLC27A1* as well as of the metabolism regulator *NCoR1*[4]. This indicates a change in excitability and a shift towards an oxidative metabolism in DLBCL, since fatty acid transporters increased levels contribute to the cell uptake of fatty acids when tumour cells downregulate glycolysis and switch to mitochondrial respiration[5].
Overall, the ICT-GEP may contribute to identifying novel lymphoma biomarkers related to excitability and metabolic pathways and could represent a novel and valuable approach for uncovering the biological and biochemical bases of lymphomagenesis and FL progression, suggesting novel possible metabolic targets for cancer therapy, with particular relevance for the drug resistance relapsed FL.

References:

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