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POSTER 8: Glutamine regulates BCR/Abl expression in hypoxic chronic myeloid leukemia cells via fatty acids metabolism

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Introduction

Under very low oxygen tension, Chronic Myeloid Leukemia (CML) cells undergo the suppression of the BCR/Abl oncoprotein, whereas a BCR/Abl-independent subset of cells, commonly referred to as leukemia stem cells, is maintained. Such cell population retains the capacity, when transferred to normoxic conditions, to generate a BCR/Abl-expressing progeny which is, *in vivo*, responsible for the relapse of the disease, demonstrating to be also resistant to the tyrosine kinase inhibitors (TKi) by lacking their molecular target. Moreover, under oxygen restriction, glutamine plays a major role, stabilizing c-Myc expression and inducing cancer cells to diverge towards a more pronounced fatty acids (FA) metabolism.

Material and Method

K562 and KCL22 cell lines were subjected to glucose and/or glutamine deprivation in hypoxic conditions (96hrs at 0.1% O2). Cells metabolic profile was generated through the Seahorse XFe96 Analyzer while L-Glutamine-13C5 was exploited via LC/MS to determine its contribution in FA *de novo* synthesis. BODIPY 493/503 was used to measure the intracellular neutral lipid droplets in confocal microscopy and flow cytometry whose presence and morphology were also determined via transmission electron microscopy. BCR/Abl was evaluated via Western Blotting whilst CD36 was determined through flow cytometry.

Results and discussion

We observed that glutamine is capable to boost glycolysis, leading to a faster BCR/Abl downregulation in hypoxic conditions, and decrease the basal and maximal cell respiration capacity. We also identified that under oxygen and glucose shortage, CML cells were characterized by numerous lipid droplets. Such an augmented neutral lipid content was due to a glutamine-dependent CD36 upregulation, which is capable to uptake FA from the extracellular milieu. In these conditions, CML cells rapidly lose BCR/Abl expression, a phenomenon which was validated by the treatment with exogenous BSA-Palmitate, capable to reduce BCR/Abl expression, while the use of the sulfosuccinimidyl oleate, a specific CD36 inhibitor, sustained the oncoprotein maintenance instead.

Conclusion

Our results suggest that FA may play a fundamental role in hypoxic-induced BCR/Abl suppression and that such FA degradation might be needed for the oncoprotein re-expression once normoxic conditions are restored. This phenomenon might be therefore exploited to sustain BCR/Abl expression in hypoxic cells to be more susceptible to TKi.