Dj1 proteoforms in breast cancer cells: the escape of metabolic epigenetic misregulation

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E. Olivo[I], C.V. Fiumara[I], V. Agosti[I], G. Cuda[I], D. Scumaci[I]

[I]University Magna Graecia of Catanzaro, Catanzaro, Italy

In cancer cells, the high glycolytic flux induces carbonyl stress, a damage that increases reactive carbonyl species making DNA, proteins and lipids more susceptible to glycation. Together with glucose, methylglyoxal (MGO), a byproduct of glycolysis, is considered the main glycating agent. MGO is highly diffusible, enters the nucleus and reacts with lysine- arginine-rich tails of histones.

Glycation adducts on histones undergo oxidization and rearrange to form stable species known as advanced glycation end-products (AGEs). This modification alters nucleosomes stability and chromatin architecture deconstructing the histone code. Formation of AGEs has been associated with cancer and several age-related diseases. DJ1, a cancer-associated protein that protects cells from oxidative stress, has been described as a deglycase enzyme. In several human tumours, its expression, localization, oxidation, and phosphorylation were found altered.

This work aims to explore the molecular mechanism that triggers the peculiar cellular compartmentalization and the specific post translational modifications (PTM) that influences the DJ1 dual role, in breast cancer cells. Using a proteomic approach, we identify on DJ1 a novel threonine phosphorylation, part of a putative Akt consensus.

Interestingly we found that pharmacological modulation of Akt pathway induces a functional tuning of DJ1 proteoforms revealing that the pathway is critical for DJ1 pro-tumorigenic abilities.
In breast cancer cells, the overactivation of Akt signaling enhances DJ1-phosphorylation. Phosphorylated DJ1 increases its glyoxalase activity thus preventing glycation-induced histones misregulation. In this work we report the characterization of a novel proteoform of DJ1 accounting to the ability of cancer cells to counteract carbonyl stress. Dj1 Glyoxalase activity is crucial for the escape of metabolic induced epigenetic misregulation that otherwise could impair the malignant proliferative potential of cancer cells.