

PGC1-Alpha and Cyclin D1 Synergistically Activate Lipogenesis via Upregulated Oxidative Pentose Phosphate Pathway and TCA Cycle Citrate Efflux

Grello, Cassandra

The ability of a cancer cell to alter its metabolic capacity was described by Warburg in the 1930s as an increase in energy production via glycolysis. Today, it is understood that transcriptional and epigenetic changes affect multiple metabolic pathways, including the TCA cycle, pentose phosphate pathway (PPP), and lipogenesis, which provide cancerous cells with enough energy and biosynthetic capacity to proliferate rapidly and resist immune attack. PGC1 α and cyclin D1 (CD1) have emerged as two important cofactors in the alteration of metabolism during tumorigenesis: the former is a transcriptional cofactor and the latter a cell cycle regulator. Mass spectrometric analysis was performed on human hepatoma cell lysates infected with adenovirus containing either PGC1 α , CD1, or a combination of both (PGC1+CD1). Citrate and, to a lesser extent, other TCA cycle metabolites were present at increased concentrations in PGC1+CD1 cells as compared to control. Relative abundance of citrate as compared to alpha-ketoglutarate and malate suggests an efflux of citrate towards the lipogenic pathway. Additionally, enhanced PPP activity is supported by RT-PCR and Western blot data demonstrating increased gene expression for both glucose-6-phosphate dehydrogenase (G6PD) and transketolase and increased protein levels of G6PD, respectively in PGC1+CD1 cells. As upregulated PPP yields NADPH for reductive biosynthesis and citrate can be readily converted to acetyl-coA, the combination of PGC1 α and CD1 may be promoting lipogenesis which would enable a cancer cell to produce fatty acids and lipids and utilize acetyl groups for histone and protein acetylation. Treatments targeting citrate metabolism and/or PPP may inhibit upregulated lipogenesis in cancer, serving as a viable tumor therapy.

Awards Won:

Fourth Award of \$500