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Lipogenesis in HER2/neu positive breast cancer cells

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Alterations in lipid metabolism have been reported in many types of cancer. Lipids have been implicated in a number of processes important to cancer cells. Recent work has shown that HER2/neu-positive breast cancer cells rely on a unique lipogenic Warburg-like metabolism for survival and aggressive behavior. These cells are dependent on fatty acid synthesis, show markedly increased levels of stored fats and disruption of the synthetic process results in apoptosis. The pathway is operating at its limits in HER2/neu-positive cells and addition of physiological doses of exogenous palmitate induces cell death. HER2-normal cells are not affected. Transcriptional profiling and computational analyses showed that palmitate induced functionally distinct transcriptional programs in HER2-normal MCF7 and HER2/neu-positive SKBR3 breast cancer cells. In HER2/neu-positive cells, palmitate activated an ER-stress response network and reduced HER2 and HER3 protein levels sensitizing the cells to treatment with trastuzumab. Global metabolite profiling data identified affected metabolic pathways and were integrated in a multi-omics network analysis. The growth of HER2-normal MCF7 cells was unaffected by exogenous palmitate although several species of neutral lipids increased as expected. The predominant upregulated lipid species in HER2/neu-positive SKBR3 cells was the novel bioactive lipid N-palmitoylglycine. In addition, the cells exhibited AMPK activation, inhibition of fatty acid synthesis and significantly altered glutamine, glucose and serine/glycine metabolism. Limiting the availability of glutamine significantly ameliorated the lipotoxic effects of palmitate reversing the transcriptional effects. Our results indicate that the lipogenic phenotype of HER2/neu-positive breast cancer cells places metabolic constraints on HER2-mediated oncogenic signaling and therapy.

Biography

Douglas S Conklin is an Associate Professor at the Cancer Research Center at the State University of New York, University at Albany. He received his Doctoral degree at the University of Wisconsin-Madison and was a Post-doctoral fellow at Cold Spring Harbor Laboratory. His research focus is on functional genomics of cancer.

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