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Targeting the unique properties of glucose in cancer through calcium-PP2A-RIPK1 pathway

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Cancer cells have enhanced glycolysis in the presence of oxygen, a phenomenon known as the Warburg effect. Unlike normal cells, cancer cells are highly dependent on glucose for survival. Therefore, it was predicted that glycolysis inhibitors would selectively eliminate cancer cells. Contrary to prediction, commercially available glycolytic inhibitors have limited response on cancer cell inhibition. To fully understand how glucose deprivation kills cancer cells, we investigated the effects of glucose deprivation on different cancer cells. We showed that demethylation of the catalytic subunit of protein phosphatase 2A (PP2A) occurs uniquely in a subset of cancer cells that are sensitive to glucose deprivation. Glucose deprivation triggers an influx of calcium into the cytoplasm activating calcium/calmodulin-dependent protein kinase, CAMK1 and in turn, the PP2Ac demethylase PPME1. PP2Ac demethylation activates receptor-interacting serine/threonine protein kinase 1 RIPK1, which induces RIPK1-dependent cell death. PP2Ac demethylation and cell death are rescued with glucose and unexpectedly, with its non-metabolizable analog, 2-deoxy-D-glucose (2-DG), a glycolytic inhibitor. These findings reveal that glucose could protect cells from cell death via the regulation of calcium signaling independent from its glycolytic properties and ATP levels. This is in sharp contrast to the current dogma of targeting the Warburg effect. We also found that after glucose removal, only a subset of cancer cells but not normal cells maintain critically low intracellular glucose levels. By targeting this unique property of glucose that is independent from glycolytic pathway, we can efficiently induce cancer cell death without affecting normal cells. Indeed, we successfully induced cell death on a subset of cancer cells but not normal cells by the combinational treatments of STF-31, a GLUT1 inhibitor that blocks the glucose transport and thapsigargin, which increases intracellular calcium concentration. Taken together, our results reveal a novel glucose sensing pathway that represents a potential therapeutic target in cancer.

Biography

Ha Yin Lee has her research focus on cancer metabolism and she has been investigating the potential therapeutic target in cancer metabolism. She has completed her graduation degree in 2015 from NUS.

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