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Targeting cancer metabolism to overcome treatment resistance in HER2-positive breast cancer

Paola A Marignani
Dalhousie University, Canada

Metabolic adaption of tumour cells is necessary to meet biosynthesis and energy needs of a growing cancer. The energy sensing kinase AMPK is responsible for maintaining AMP/ATP ratio, serving as a metabolic checkpoint that is activated when phosphorylated by the LKB1, a tumour suppressor kinase. LKB1 is frequently found mutated in numerous cancers including 31% of HER2 breast cancer. In our LKB1-/-NIC model, loss of LKB1 expression resulted in reduced tumour latency where tumours were biochemically characterized as hyperactive mTOR, along with metabolic changes characteristic of Warburg effect, namely elevated ATP, LDH, PDH expression and enhanced lactate. Based on these finding, we conducted a pre-clinical studies to evaluate novel combinatorial therapies on tumourigenesis. We report that targeting PI3K-p70S6K pathways with competitive NVP-BEZ235 inhibitor was not as effective at reducing tumourigenesis as targeting mTOR and glycolysis with AZD8055 and 2-DG monotherapies, respectively. Interestingly, simultaneous inhibition of these pathways with AZD8055/2-DG combination was significantly more effective at reducing mitochondria function, tumour volume and burden, culminating in reduced tumourigenesis. At the molecular level, combination treatment inhibited both mTOR signalling and blocked MAPK survival signalling that is responsible for ERK-p90RSK pathway engagement. Finally, loss of LKB1 expression in cancers should be considered a marker for metabolic dysfunction given the role LKB1 plays in regulating both AMPK activity and mTOR function. The results of our pre-clinical studies suggest that combinatorial therapy that target mTORC1/mTORC2 and glycolytic pathways in cancer, is critical for inhibiting tumour growth. Importantly, our discovery showed that the drug combination inhibited the activation of feedback loops that are drivers of resistance, namely ERK and p90RSK. We believe that simultaneous targeting of these pathways will provide the best clinical outcome for the treatment of metabolically active cancers, as well as reduce the likelihood of recurrence.

Biography

Paola Marignani received her PhD from McMaster University, followed by Postdoctoral fellowships at Harvard, the Samuel Lunenfeld Research Institute and the Ontario Cancer Institute. The Marignani Discovery Research Laboratory uses animal models and high through-put screening strategies to identify novel signalling pathways involved in disease. Marignani and her team have shown that the tumour suppressor kinase LKB1 is an interacting partner and regulator of the estrogen receptor. More recently her team developed a novel spontaneous mouse model of breast cancer. In this model, proteomic and metabolic profiling of tumours confirm hyperactive mTOR and metabolic activity. By combining multiple platforms, The Marignani Discovery Research Laboratory continues to focus on identifying molecular switches that drive tumourigenesis, conduct pre-clinical trials that evaluate novel targeted therapies and develop clinically relevance animals models of human disease.

Paola.Marignani@Dal.Ca

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