# Accumulation of Methylglyoxal, a glycolysis by-product, modulates YAP1 transcription co-factor localization and activity in human breast cancer cells through HSP90 modification

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Methylglyoxal (MG), a highly reactive glycolysis by-product, is accumulated in tumor cells where it glycates proteins. In our recent publication, we detected MG-protein adducts in breast cancer cells using immunohistochemistry and immunoblotting. In this study, we wanted to characterize further MG-modified proteins and explore their impact on breast cancer cells. Yes-associated protein 1 (YAP1) is a transcription co-factor involved in the regulation of cellular growth, proliferation and apoptosis that is overexpressed in cancer cells. Upon cell confluence, YAP1 is phosphorylated by LATS1, a serine/threonine kinase of the Hippo pathway and exported out of the nucleus. HSP90 contributes to cell homeostasis by regulating conformational maturation of many kinases including LATS1.

MG treatment led to a significant accumulation of YAP1 both in the nucleus and the cytoplasm of confluent human breast cancer cells compared to untreated cells. We further confirmed MG-induced nuclear YAP1 activity on Connective Tissue Growth Factor (CTGF) expression, a well described YAP1-mediated pro-tumoral effect. Indeed, in combination with TGFß, MG treatment increased YAP1-mediated expression of CTGF above the level induced by TGFß alone in breast cancer cells. We demonstrated that MG treatment reduced HSP90 expression in breast cancer cells. This downregulation is associated with a decrease of LATS1 and phosphorylated YAP1. Finally, we showed, using mass spectrometry, that HSP90 is a direct target of MG in breast cancer cells. Ongoing immunohistochemistry experiments will help us to determine a potential correlation between YAP1, HSP90 and MG-adducts levels in human breast cancer tissues.

Our identification of a new MG target in cancer cells and the subsequent regulation of the Hippo pathway, one of the major tumor suppressor signaling pathways, represent the first indication of the pro-tumorigenic effect of this highly reactive endogenous metabolite accumulated in tumors.

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