Response to Comment on: Winkler et al. Histone Deacetylase 6 (*HDAC6*) Is an Essential Modifier of Glucocorticoid-Induced Hepatic Gluconeogenesis. Diabetes 2012;61:513–523

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In his letter (1), Mahla proposes the combination therapy of histone deacetylase 6 (HDAC6) and heat shock protein 90 (HSP90) inhibitors as an antitumor strategy. This proposal is based on previous publications demonstrating that HDAC6 deacetylates HSP90, thereby modulating the activity of HSP90 client proteins. Pharmacological inhibition of HSP90 has been shown to serve as a potential anticancer approach. In addition, HDAC6 regulates multiple pathways involved in tumorigenesis, and HDAC6 inhibitors are currently developed for cancer therapy.

We recently showed that HDAC6 serves as a crucial modifier of glucocorticoid (GC)-mediated hepatic gluconeogenesis (2). Inhibition of HDAC6 activity results in impaired glucocorticoid receptor (GR) translocation and subsequent attenuation of GR-dependent gluconeogenic target gene regulation (2). Furthermore, loss of HDAC6 activity attenuated GC-GR–mediated impairment of systemic insulin and glucose metabolism (2).

Pharmacological targeting of tumor cell metabolism, in particular glucose metabolism, is a highly active field of current cancer research (3). Given the close molecular interaction between HSP90 and HDAC6, and their given potential as antitumor targets, we agree with the comment of Mahla that a combination of HDAC6 and HSP90 inhibition may be a promising synergistic antitumor approach. However, certain important issues have to be taken into account: *1*) Our experiments focused on metabolic actions induced by an exogenously provided GC; additional experiments are required to clarify whether these processes also translate to the endogenous GC-GR axis, in particular in situations of pathological GC levels. *2*) Our work was predominantly performed in hepatocytes or murine liver samples; the metabolic role of HDAC6 in other tissues and organs would require future studies. *3*) Tissue/cell selectivity of the proposed combination therapy would be required; whether this will be achieved by solely decreasing the dose of a potential HDAC6 inhibitor, as proposed by Mahla, needs to be clarified.

Taken together, given the importance of targeting cancer cell metabolism for antitumor therapy, pharmacological inhibition of HDAC6 in combination with HSP90 may be a promising new therapeutic approach; however, the unanswered questions need to be addressed.

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REFERENCES

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