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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Histone deacetylase 6 (HDAC 6) is known to play a critical role in histone modification and transcription regulation of a wide variety of genes involved in cell cycle regulation and cell proliferation, migration, and development. Recently, Winkler et al. (1) analyzed the role of HDAC6 in regulation of metabolism-mediating transcription of gluconeogenic genes *G6P*, *FBP*, *PEPCK*, and *PCX* through glucocorticoid receptors. HDAC6 is known to deacetylate histone and nonhistone proteins including molecular chaperone heat shock protein 90 (Hsp90). Since Hsp90 has an active conformation with its client protein in cancerous cells, targeting this conformation destabilizes the client proteins involved in cell proliferation; this is considered a potential approach for cancer treatment, and thousands of drugs have come into the picture, some of which are used in clinics. Lee et al. (2) reported that HDAC6 plays a critical role in oncogenic transformation, and many cancer cell lines express HDAC6 in high amounts. It has not been reported that HDAC6 has a different conformational status in the case of cancer or disease, so targeting this HDAC6 cannot discriminate between normal or diseased cell. As such, using a low dose of HDAC6 inhibitor in combination with Hsp90 inhibitor can be a potential therapeutic approach, where HDAC6 inhibitor can slow down metabolism while Hsp90 inhibitor makes the client protein prone to degradation. At the same time, HDAC6 is known to play a critical role in the clearance of unfolded protein, assisted through autophagy. In the present scenario, application of HDAC6 inhibitor either alone or in combination needs to be explored to target diseases such as cancer.

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REFERENCES

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