role of HDAC3 as a transcriptional repressor.

A machine-learning approach revealed DNA sequences associated with DA-dependent and DA-dependent genomic regions bound by HDAC3 that could predict transcriptional outcome. In particular, binding of the co-factor ATF2 was associated with DA-dependent sites whereas ATF3 binding was associated with DA-dependent sites. In keeping with this, LPS stimulated the transcription of a DA-dependent reporter gene containing the ATF2 motif in the presence of ATF2 and inactive HDAC3, whereas LPS-mediated repression of a DA-dependent reporter gene with the ATF3 motif required ATF3 and wild-type HDAC3. Transcriptional activation by HDAC3 required the transcription factor p65, which was recruited to DA-independent sites by LPS. Deacetylase-dependent transcriptional repression by HDAC3 required the co-repressors NCoR1 and NCoR2, which were recruited to DA-dependent sites enriched for ATF3 binding.

Thus, HDAC3 can switch between activation and repression of target genes dependent on co-factor recruitment, which can promote or inhibit the inflammatory response to LPS, respectively. Mice with reduced catalytic activity of HDAC3 were more susceptible to a lethal dose of LPS, with higher levels of pro-inflammatory cytokines, whereas mice lacking HDAC3 were protected from LPS toxicity. These opposing roles of HDAC3 will need to be considered in the clinical use of HDAC inhibitors.