Can histone deacetylase inhibitors be used as additional adjunct in trauma hemorrhagic shock?

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Trauma remains a significant public health issue in all age groups. 50% of the trauma patients die in the first 24 hours of Trauma hemorrhagic Shock (T/HS), a condition with no therapeutic option till date. Severe HS initiates an inflammatory cascade that increases the patient's risk of immunological dysfunction, systemic inflammation (SIRS), multi-system organ failure and sepsis.[1]

In the T/HS, inflammatory genes are well studied. However, mechanisms of chromatin remodelling are not much studied. At the molecular level, it has been reported that both hemorrhage and sepsis leads to epigenetic changes inside the cell. In both cases, there is an imbalance in acetylation of histone proteins.[2] The chemical modifications on the amino-terminal tails of histones, namely, acetylation, methylation, ubiquitination, and phosphorylation are associated with conformational changes in chromatin structure.[3] Among them, an open chromatin structure is generated by the acetylation of histone tails which contributes to active transcription. Acetylation is regulated by two types of proteins– HATs (Histone Acetyl Transferases) and HDACs (Histone Deacetylases).[3]

Inducible histone modifications have been shown to exert control of innate and adaptive immune responses, in both, humans as well as animal models. These histone modifications have been shown to specifically target NF-κB regulation.[4] They either directly inhibit gene transcription or indirectly through modulation of nuclear transcription factors such as NF-κB.[5] NF-κB activation leads to the production of proinflammatory cytokines like TNF-alpha and IL-1 β. HDAC1 and HDAC2 have been shown to down regulate the NF-κB family-mediated gene transcription. HDAC enzymes are therefore critical in the balance of inflammatory responses by regulating the histone acetylation status of NF-κB gene.[5] The functions of macrophages are also regulated by histone modifications. In particular, activation of Toll-like receptor (TLR) signalling in macrophages induces histone acetylation at lysine residues of inflammatory cytokine genes.[3]

Some studies have been done on expression levels of HDACs and histone acetylation of T/HS. Li et al. showed that the suppression of HDACs activity and blockade of NF-κB signalling during resuscitation improves microvascular endothelial proinflammatory responses in organs in mice after hemorrhagic shock.[6] Treatment with VPA (Valproic acid), an HDACI (Histone Deacetylase Inhibitor) increased acetylation at H3K9 residues in kidney cells of mice which suffered lethal hemorrhagic shock.[7] Also, VPA treatment reduces inflammation in cerebral tissue after TBI/HS and induces pathways involved in wound repair. In mouse, VPA has been shown to increase survival rate after hemorrhagic shock. It activated PI3K-Akt-GSK-3β survival pathways.[8] Sailhamer et al. showed that there is a decrease in the baseline level of acetylation of human leukocytes of spleen the following polytrauma with splenic injury. Another HDACI, SAHA (Suberoylanilide hydroxamic acid) reduces inflammatory cytokines levels of spleen leukocytes in humans. The cytokine levels were reduced by non-nuclear proteins acetylation.[9]

So far, these studies have shown to pro-survival effects in T/HS. However, in humans, no study has been done to see the effects of HDACI in T/HS. The author feels that this subject needs to be attended.

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