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Cathepsin B is a Validated Drug Target for Traumatic Brain Injury (TBI) and TBI-Related Brain Disorders

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There currently are no or limited pharmaceutical treatments for traumatic brain injury (TBI) and the related conditions of ischemia, epilepsy, inflammatory pain, Alzheimer's disease (AD) and multiple sclerosis (MS). Why that is the case is not clear but it could be because the current molecular targets used to develop drugs for these conditions are not targets that are able to significantly improve the disease. As such, there is a need to discover new drug targets from which more effective therapies may emerge. This presentation summarizes the genetic knockout data on the cysteine protease, cathepsin B, showing that deleting this gene provides multiple beneficial outcomes in TBI and related conditions. Specifically, cathepsin B deficient animals that suffer TBI have significantly improved neuromotor dysfunction and reduced brain tissue loss and neuronal cell death than do sufficient animals. In an ischemic model, cathepsin B knockout animals have significantly less brain damage and inflammatory cytokine production than do wild-type (wt) animals. In an epilepsy model, animals lacking cathepsin B have significantly reduced brain neuronal cell death by apoptosis than do those expressing cathepsin B. In an inflammatory chronic pain model, cathepsin B knockout mice have reduced chronic pain and inflammatory cytokine production than do wt mice. In transgenic AD mice expressing human APP containing the wt β-secretase site sequence and London mutation, deleting the cathepsin B gene improves memory deficits and reduces neurotoxic brain amyloid-β. In a MS model, the double deletion of cathepsin B and another cysteine protease, cathepsin S, results in much improved MS clinical scores, delayed age of onset, and reduced lymphocyte infiltration into the spinal cord than that which occurs in wt mice. Moreover, clinical data shows that plasma cathepsin B is elevated in polytrauma patients and that higher plasma cathepsin B levels correlate with the trauma severity; further, plasma cathepsin B levels are higher in AD patients than controls and that higher plasma cathepsin B levels correlate with reduced cognitive capability. These data validate cathepsin B as a new drug target for TBI and related brain disorders and suggest that compounds, which inhibit cathepsin B's proteolytic activity, are likely to reduce brain neuronal cell death and inflammation and thereby provide effective treatment for these TBI and related conditions.