HMGB1

HMGB1 is an intracellular DNA binding protein.

The aim of the study was to assess changes in high mobility group box protein 1 (HMGB1) expression in epileptic patients with and without comorbid depression. Sixty patients with drug-resistant temporal lobe epilepsy who underwent anterior temporal lobectomy were enrolled. Anterior hippocampal samples were collected after surgery and analyzed by immunofluorescence (n = 7/group). They also evaluated the expression of HMGB1 in TLE patients with hippocampal sclerosis and measured the level of plasma HMGB1 by enzyme-linked immunosorbent assay. The results showed that 28.3% of the patients (17/60) had comorbid depression. HMGB1 was ubiquitously expressed in all subregions of the anterior hippocampus. The ratio of HMGB1-immunoreactive neurons and astrocytes was significantly increased in both TLE patients with hippocampal sclerosis and TLE patients with comorbid depression compared to patients with TLE only. The ratio of cytoplasmic to nuclear HMGB1-positive neurons in the hippocampus was higher in depressed patients with TLE than in non-depressed patients, which suggested that more HMGB1 translocated from the nucleus to the cytoplasm in the depressed group. There was no significant difference in the plasma level of HMGB1 among patients with TLE alone, TLE with hippocampal sclerosis, and TLE with comorbid depression. The results of the study revealed that the translocation of HMGB1 from the nucleus to the cytoplasm in hippocampal neurons may play a previously unrecognized role in the initiation and amplification of epilepsy and comorbid depression. The direct targeting of neural HMGB1 is a promising approach for anti-inflammatory therapy [1)]

In a study, Shah et al. from Columbia University, New York, The Feinstein Institute for Medical Research, Northwell Health, Manhasset, NY, Hempstead, NY, Department of Neurosurgery, Hofstra Northwell School of Medicine, Hempstead, NY, USA and Department of Molecular Medicine, Hofstra Northwell School of Medicine, Hempstead, NY, USA, showed that HMGB1 and IL-6 levels increase in patients with advanced Intervertebral disc degeneration (DD) in comparison to early DD. This study further tested the hypothesis that HMGB1 promotes inflammatory signaling driving DD in human nucleus pulposus (NP) cells and tissue. Immunofluorescence and western blot analysis confirmed the expression of HMGB1 and its extracellular release by NP cells under cell stress. Gene expression and protein quantification indicate that HMGB1 stimulates the expression IL-6 and MMP-1 in a dose-dependent manner. The contributions of toll like receptor (TLR) -2, -4 and receptor for advanced glycation end products (RAGE) as receptors mediating HMGB1 signaling was examined using small molecule inhibitors. Inhibition of TLR-4 signaling, with TAK-242, completely abrogated HMGB1 induced IL-6 and MMP-1 expression, whereas inhibition of TLR-2, with O-vanillin, or RAGE, with FPS-ZM1, had mild inhibitory effects. HMGB1 stimulation activated NF-kB signaling while TAK-242 co-treatment abrogated it. Lastly, effects of HMGB1 on matrix deposition was evaluated in a 3D culture system of human NP cells. These results implicate HMGB1 as a potent DAMP that promotes inflammation in NP cells and degradation of NP tissues. TLR4-HMGB1 axis is a potential major pathway to alleviate disc inflammation and mitigate DD [2)].

Function

Important in chromatin remodeling which can be released by necrotic cells passively and by active secretion from macrophages, natural killer (NK) cells and dendritic cells.

High-mobility group box 1 protein (HMGB1), which previously was thought to function only as a nuclear factor that enhances transcription, was recently discovered to be a crucial cytokine that mediates the response to infection, injury and inflammation. These observations have led to the emergence of a new field in immunology that is focused on understanding the mechanisms of HMGB1 release, its biological activities and its pathological effects in sepsis, arthritis, cancer and other diseases.

Lotze et al., discuss these features of HMGB1 and summarize recent advances that have led to the preclinical development of therapeutics that modulate HMGB1 release and activity [3].

Following TBI, HMGB1 is released from damaged neurons and is elevated in patient's serum and CSF. Furthermore, studies showed the potential for HMGB1 to serve as a prognostic biomarker and therapeutic target in patients with TBI. Thus, HMGB1 is a prospective candidate for future studies as it shows promise in treating and/or predicting the sequelae of TBI [4].

Mirroring Enoxaparin (ENX), HMGB1 signaling blockade reduces LEU recruitment, cerebrovascular permeability, and cerebral edema following TBI. ENX further reduced lung edema indicating a multifaceted effect beyond HMGB1 blockade. Further study is needed to determine how ENX may play a role in blunting HMGB1 signaling in brain injury patients [5].

1)
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