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Peroxiredoxin family protein is a key initiator of the cerebral post-ischemic inflammation

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Abstract

Post-ischemic inflammation is an essential step for the progression of ischemic brain injury. We have discovered that peroxiredoxin (Prx) family protein is released from dying brain cells and plays a pivotal role in the activation of infiltrating immune cells. High mobility group box 1 (HMGB1) is another danger-associated molecular patterns (DAMPs) in cerebral ischemic injury; however, extracellular release of HMGB1 is diminished within 6 h after stroke onset. Since blood immune cells begin to infiltrate into the ischemic brain thereafter, a direct effect of HMGB1 on infiltrating immune cells is limited. We have identified Prx in brain lysate as a strong inducer of inflammatory cytokines in bone marrow derived dendritic cell (BMDC). As Prx is originally an anti-oxidant protein within brain cells, fatally wounded brain cells express Prx strongly, and such an intracellular Prx makes a neuroprotective effect. When ischemic phenomena finally results in necrosis of brain cells, Prx is released into the extracellular compartment and functions as DAMPs. In fact, extracellular release of Prx is observed 12 – 24 h after stroke onset and strongly stimulates TLR2 and TLR4, which is due to the common alpha 3-helix region of Prx. Anti-Prx neutralizing antibody suppresses inflammatory cytokines expression in infiltrating macrophages and infarct volume growth. Thus, Prx family proteins are considered to be essential DAMPs in cerebral ischemic injury.