Discovery of prothymosin alpha, which inhibits ischemia-induced neuronal necrosis

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A stroke delivers necrosis near the clot (ischemic core), which is triggered by ATP scarcity. We initially identified a nuclear protein, prothymosin alpha (ProTα), as a key protein inhibiting necrosis by subjecting conditioned media from serum-free cultures of cortical neurons. Recombinant ProTα reversed the rapid decrease in survival activity in cortical neurons caused by serum-free stress or low-oxygen, low-glucose type (LOG) ischemia-reperfusion stress. The addition of ProTα abolished all the typical necrotic features in the TEM analysis. ProTα inhibited the necrosis of cultured neurons by preventing rapid loss of cellular ATP levels via a reversal of decreased membrane localization of glucose transporters. This mechanism needs to activate on $G\alpha_{i/o}$-PLC-PKC pathway. Moreover, knockdown of $PKC\beta_{II}$ but not PKCα and β_I expression prevented this membrane localization.

Systemic administrations of recombinant ProTα at 30 min and 3 h after reperfusion, largely inhibited the *in vivo* focal ischemia (transient MCAO)-induced brain damages (necrosis and apoptosis), motor dysfunction and lethality. ProTα-induced neuroprotective effects significant maintained treatment of 7 h after ischemic stress. On the other hand, ProTα treatments also protected motor dysfunction and lethality in permanent MCAO model. Thus, it is expected that ProTα may have an overall neuroprotective roles in the treatment of stroke.