

HuR Regulation of HSP70 Expression During Brain Reperfusion

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Brain damage after ischemia and reperfusion (I/R), as occurs following stroke (focal ischemia) or cardiac arrest and resuscitation (global ischemia), is clinically untreatable because the mechanisms underlying cell death are not fully understood. Ischemia-resistant neurons, those that survive I/R, translate the inducible form of the 70 kDa heat shock protein (HSP70). Production of HSP70 is thought to be a protective response of neurons to I/R injury. Ischemic-vulnerable neurons that will die after I/R do not translate HSP70 or at least translate it much later than resistant neurons. However, the hsp70 mRNA is highly expressed in both ischemia-resistant and ischemia-vulnerable regions. The reason hsp70 mRNA is not translated to protein in vulnerable neurons is not understood. We show preliminary data that implicates the protein HuR in posttranscriptional control of hsp70 mRNA during reperfusion. HuR is an mRNA binding protein (mRBP) that specifically binds AREs (adenine and uridine rich elements) in the 3' untranslated region of a subset of mRNAs expressed after cell stress. The hsp70 mRNA contains an ARE sequence. Our preliminary data shows: (1) both vulnerable CA1 and resistant CA3 neurons transcribe large quantities of hsp70 mRNA starting at 8 hr reperfusion after 10 min of normothermic global forebrain ischemia, (2) CA3 translates HSP70 protein at 8 hr reperfusion, but CA1 does not translate it until 30 hr reperfusion, (3) HuR exports from the nucleus of hippocampal CA3 but not CA1 neurons by 8 hr reperfusion, (4) the translation of HSP70 correlates precisely with the formation of granules of HuR in the cytoplasm of neurons, and (5) hsp70 mRNA co-immunoprecipitates (co-IP) with HuR from reperfused brain homogenates. We interpret this data to suggest that HuR plays a key role in nuclear export of hsp70 mRNA.

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