Stress-Induced Modulation of Human Antigen R by the Apoptosis Mediator Cytochrome c and Tyrosine Kinase JAK3

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The post-transcriptional control of gene expression is mediated by the so-called RNA-binding proteins (RBPs). One of the best studied RBPs is the Human antigen R (HuR), which usually enhances the stability and translation of its mRNA ligands. Moreover, HuR binds to the histone chaperone ANP32B to export cargo mRNAs into the cytoplasm. Our group is currently developing two lines of research on the regulation of HuR function. The first one originated from pull-down assays in which we had detected the association of the apoptosis mediator cytochrome *c* (C*c*) with HuR upon DNA damage stimulus. Interestingly, we already had evidence suggesting a physiologically relevant interaction between ANP32B and C*c*. Therefore, our ongoing investigation aims to elucidate whether C*c* directly binds to HuR or, alternatively, ANP32B acts as a molecular bridge linking the other two proteins. Furthermore, we are also examining the biological significance of the above-mentioned interactions in the context of programmed cell death. On the other hand, our second research line focuses on the role of Janus kinase 3 (JAK3) in the modulation of HuR binding to cognate mRNAs. Indeed, stress-induced phosphorylation of HuR at Tyr200 by JAK3 has been related to a reduced interaction of this RBP with its target transcripts. To get a deeper insight into this observation, we mimicked Tyr200 phosphorylation by co-expressing a tRNA/aminoacyl-tRNA synthetase pair specific for the non-canonical amino acid *p*-carboxymethyl-L-phenylalanine (*p*CMF) together with an HuR construct. Through several biophysical assays with phosphomimetic Y200*p*CMF HuR and single-stranded DNA oligonucleotides, we want to assess the impact of JAK3 activity on HuR affinity for mRNA. Importantly, HuR is considered an oncoprotein and its dysregulation has been implicated in several diseases. Thus, a better understanding of the molecular mechanisms controlling HuR function could provide valuable data for the design of new therapies.