Post-transcriptional regulation of tumour necrosis factor $\alpha$ production

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Tumour necrosis factor $\alpha$ (TNF$\alpha$) is a proinflammatory cytokine produced by activated macrophages, lymphocytes and other cells.\(^1\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(^,\)\(...
Mutant mice lacking TIAR exhibit partial embryonic lethality and defective germ cell maturation, implicating this protein in selective aspects of vertebrate development.17

The discovery of TIAR as a component of the ARE associated complex that assembles on the 3' UTR of TNFα transcripts14 provided the first clue that TIA-1 and TIAR might specifically regulate the expression of TNFα. To test this hypothesis, we produced mutant mice lacking TIA-1 and compared the LPS induced expression of TNFα in wild type and TIA-1/-/- macrophages.18 Our results indicate that LPS induced expression of TNFα is significantly increased in macrophages lacking TIA-1.19 The functional effects of TIA-1 seem to result from translational silencing rather than regulation of mRNA stability.18 Thus, the ARE binding protein TIA-1 represses the expression of TNFα by a mechanism that differs from that used by other known ARE binding proteins.

Although both TIA-1 and TIAR are concentrated in the nucleus at steady state, heterokaryon analysis shows that both proteins continuously shuttle between the nucleus and the cytoplasm (Kedersha and Anderson, manuscript in preparation). In this respect, TIA-1 and TIAR resemble the heteronuclear ribonucleoproteins (hnRNPs) that assemble around nascent RNA transcripts and facilitate transport from the nucleus to the cytoplasm.20 Like the hnRNPs, TIA-1 and TIAR can function as general RNA binding proteins that interact with many, if not most, mRNAs in vitro.21 At the same time, these proteins can selectively interact with RNAs possessing uridine-rich motifs.22 In their ability to function as both general and specific RNA binding proteins, TIA-1 and TIAR resemble hnRNPs K and E1, proteins that participate in general RNA export and also bind to the 3' UTRs of 5'-lipoxygenase transcripts to repress translational initiation.23,24

Conclusions

Our results introduce TIA-1 and TIAR as translational silencers that can independently and selectively regulate the production of TNFα. Previous studies using macrophage cell lines have clearly shown that translational silencing is important in the post-transcriptional control of TNFα production.25,26 In the unstimulated macrophage cell line RAW 264.7, TNFα transcripts are expressed but excluded from polysomes and not translated.27 Comparison of TNFα mRNA distribution into polysomes in wild type and TIA-1/-/- macrophages indicate that TIA-1 controls the association of TNFα mRNA with polysomes. It remains to be determined whether TIA-1/R induced translational silencing is achieved by regulation of translational initiation. In any case, the ability of TIA-1 and TIAR to inhibit TNFα mRNA translation suggests that these proteins might be targets of the stress kinase signalling cascade that is blocked by CSAIDS. CSAIDS block the LPS induced production of TNFα by preventing translational de-repression.28 This is accomplished by inhibiting the p38-MK2 signalling cascade,29-31 suggesting that these kinases phosphorylate a translational silencer that associates with TNFα transcripts. The ability of CSAIDS to similarly repress the expression of TNFα in wild type and TIA-1/-/- macrophages indicates that TIA-1 is not an essential target of these drugs. TIA-1 might thus act as a constitutive translational suppressor controlling excessive TNFα production. Alternatively, the functional redundancy of TIA-1 and TIAR leaves open the possibility that cells lacking both TIA-1 and TIAR might be resistant to the suppressive effects of CSAIDS.

Taken together, our results suggest that TIA-1 and TIAR are translational silencers that regulate the cellular and organismal response to stress. At the cellular level, these proteins contribute to the general translational arrest that accompanies environmental stress. By controlling the duration of translational arrest, TIA-1 and TIAR might determine whether stressed cells live to repair the stress induced damage or die by apoptosis. At the organismal level, these proteins regulate the expression of at least one inflammatory mediator that serves as a sentinel to signal the presence of microbial infection. It remains to be determined whether the translational control exerted by these proteins is limited to the stress response, or is a general feature of normal cellular metabolism.
Regulation of TNFα production

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