

The importance of phosphorylation in modulating Hsp70 function; potential for novel therapeutic strategies for cancer and amyloid diseases

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Research Abstract

The role of molecular chaperones [proteins that help other proteins to fold into their functional 3D structures] in maintaining protein homeostasis and contributing to the prevention of a variety of human disease is well established. Of particular significance is the role of molecular

chaperones such as heat shock protein 70 (Hsp70) and heat shock protein 90 (Hsp90) in aspects of cancer and amyloid [such as Alzheimer's and Parkinson's] disease progression. Hsp70 and Hsp90 have been investigated as therapeutic targets for tackling these socio-economically important diseases. However, there is a caveat in that these chaperones also carry out essential cellular functions, so targeting them directly with drugs can have major consequences for cell survival and hence produce severe side effects. Recent results have demonstrated that post-translational modification [PTM], such as the addition of phosphate groups to specific amino acid residues [phosphorylation] in Hsp70 and Hsp90, can modulate chaperone function within the cell. The fact that PTM plays a major role in functionality of these chaperones offers the potential for new therapeutic strategies for cancer and amyloid diseases by indirectly targeting Hsp70 and Hsp90 through the proteins [kinases or phosphatases] that modify them. This strategy could specifically target chaperone functions that are unrelated to essential roles in the cell and thus produce therapies with reduced or no side effects. Recent studies have identified a threonine residue [T492] in the peptide-binding domain of Hsp70 as being phosphorylated and this PTM s having significant effects on chaperone function. This proposal seeks to take an interdisciplinary approach to assessing the functional significance of T492 phosphorylation in Hsp70 and the resultant consequences for the cell. This study will underpin the development of future therapies focussed on targeting Hsp70 PTM as a potential therapy for debilitating and socio-economically important diseases such as cancer, Alzheimer's and Parkinson's.

Further information available at:

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