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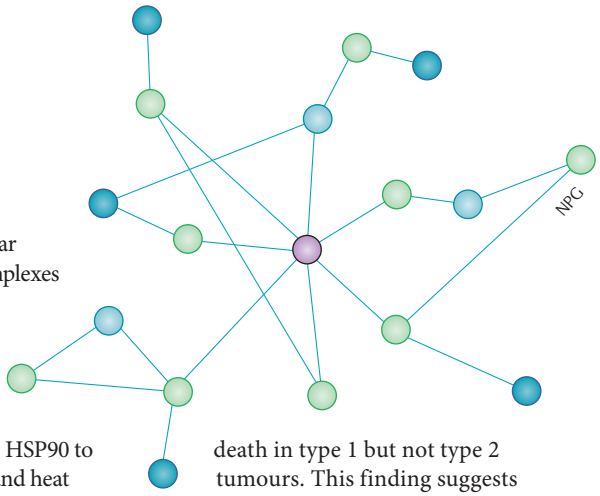
TUMORIGENESIS

Networking: a survival guide



The 'chaperome' is a multi-protein complex, comprising several protein families including chaperones and co-chaperones, which are dynamically organized into a functional network that serves to regulate proteostasis in a cell. Although chaperome components are often studied individually, few data are available on how the chaperome works as a whole in native tumours during disease progression. Now, a study by Rodina *et al.* has provided novel insight into the chaperome of cancer cells.

In the past, the chaperome has been notoriously difficult to analyse in its endogenous state, as classical protein chromatography methods are inefficient at separating chaperome complexes of similar size and composition. To overcome this issue, the authors used a platform that combines isoelectric focusing (IEF) with immunoblotting, thereby allowing multimeric protein complexes to be separated based on their isoelectric point (pI). Using this methodology revealed that the most common chaperome member in human cells, heat shock protein 90 (HSP90), was present in several different complexes with pI ranging from 4.5 to 6 across a panel of cancer cell lines and primary tumours. This contrasted with non-transformed cells in which HSP90 was identified as a single species at the expected pI of 4.9.

Further investigation revealed that these cancer cell lines could be subdivided on the basis of the differing HSP90 complexes: those enriched in HSP90 complexes with an unusually high pI of ≥ 5, termed 'type 1' tumours by the authors, and those that predominantly contained HSP90 complexes with a pI < 4.9, the 'type 2' tumours. Accounting for the pI change in type 1 tumours, the authors identified high molecular weight, multimeric complexes of HSP90 with other important chaperome components, such as HSP70–HSP90 organizing protein (HOP), which connects HSP90 to the HSP70 machinery and heat shock cognate 70 kDa protein (HSC70), in type 1 but not type 2 or non-transformed cells.

> "more than half of all cancer subtypes tested had medium to high levels of these larger chaperome complexes, irrespective of tissue of origin or genetic background"

The authors characterized the chaperome present in type 1 tumours in more detail by using an HSP90 inhibitor, PU-H71. Compared with type 2, type 1 tumours were more sensitive to PU-H71; the inhibitor also bound to HSP90 more tightly in type 1 tumours, consistent with the recognized ability of PU-H71 to bind to HSP90 more strongly when it is within a complex. The chaperome of type 1 tumours was found to be biochemically different from that of type 2 tumours not only in composition and abundance of proteins but also in the connectivity of the chaperome complexes. Although HSP90 was functional in both tumour types, only type 1 tumours formed multiple, stable networks physically integrating the HSP90 and HSP70 machinery complexes, in what the authors term the epichaperome. In contrast, chaperome complexes were not tightly integrated in type 2 tumours and were present as singular chaperome machineries forming transient interactions.

In demonstrating a requirement for the epichaperome in cancer cells, Rodina and colleagues observed that knockdown of either HSP90 or individual chaperome components or treatment with PU-H71 was able to disrupt multimeric chaperone complexes, such as that of HSC70 and induce cell death in type 1 but not type 2 tumours. This finding suggests that an intact epichaperome is necessary for survival in type 1 tumours. Given that the chaperome functions in response to stress, the authors analysed the proteome of type 1 and 2 tumours to deduce that MYC could be one of the major factors behind the epichaperome assembly. Consistent with this idea, MYC transcriptional activity was increased in type 1 tumours and the expression of *MYC* in type 2 tumours was sufficient to convert these tumours into type 1.

Lastly, Rodina *et al.* investigated the frequency of epichaperome complexes in patients with pancreatic, gastric, lung and breast cancers as well as lymphomas and leukaemias. Strikingly, more than half of all cancer subtypes tested had medium to high levels of these larger chaperome complexes, irrespective of tissue of origin or genetic background, and epichaperome expression was positively correlated with sensitivity to PU-H71-induced cytotoxicity. This study not only highlights how targeting the epichaperome, rather than individual chaperome components, might be a more successful therapeutic strategy but also hints that malignant transformation could drive the formation of other large, stable higher-order complexes to promote survival.

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ORIGINAL ARTICLE Rodina, A. *et al.* The epichaperome is an integrated chaperome network that facilitates tumour survival. *Nature* **538**, 397–401 (2016)