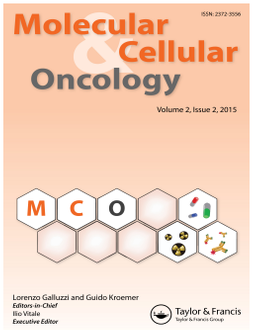

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Aneuploidy and proteotoxic stress in cancer

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Although nearly ubiquitous in cancer, aneuploidy exerts detrimental effects on human cells. We recently demonstrated that aneuploid human cells exhibit impaired heat shock factor protein 1 (HSF1) and HSP90 function, suggesting a functional link between two recurring features of cancer cells: aneuploidy and proteotoxic stress. Further, our findings implicate HSF1 as a key factor in mitigating the effects of aneuploidy.

Although the spectrum of mutations and alterations in cancer cells is extremely complex, all cancers exhibit common characteristics or hallmarks, as first proposed by Hanahan and Weinberg.[1] In a paper published in 2009, Elledge and colleagues made a compelling case that, in addition to the classic hallmarks of cancer, diverse forms of cellular stress such as proteotoxic stress and high levels of DNA damage represent unifying characteristics of established malignant cells.[2] This novel paradigm for understanding tumorigenesis and cancer treatment posits that the stress phenotypes of tumors lead to the addiction of cancer cells to pathways and molecules that ameliorate cell stress. However, how these stress phenotypes arise in cancer is not yet fully understood.

Proteotoxic stress and constitutive activation of the heat shock factor protein 1 (HSF1)-regulated heat shock response (HSR) pathway are among the recurring features of malignant cells, and inhibition of molecular chaperones represents a promising therapeutic strategy for cancer treatment.[3] It has been proposed that the heavy reliance of cancer cells on protein-folding factors stems from the role of chaperones in mitigating the stress associated with tumor development and from the large number of chaperones required to stabilize critical mutated oncogenes, although there may be additional explanations for these characteristics of cancer cells.

Aneuploidy, or an imbalanced karyotype, is nearly ubiquitous among cancer cells and has previously been proposed to be responsible for the proteotoxic stress of tumors.[2] Analysis of model yeast aneuploids has provided compelling evidence that aneuploidy elicits proteotoxic stress and impairs cellular protein folding.[4] However, until recently it has been difficult to directly study the effects of aneuploidy in metazoans and thus mechanistic evidence supporting this hypothesis in human cells has been lacking. We previously established and characterized model human aneuploid cells that differ from their cognate diploids only by the presence of additional chromosomes.[5] Using luciferase-based protein folding sensors that are exquisitely sensitive to cellular protein folding capacity in general, and to heat shock protein 90 (HSP90) function in particular, we observed striking impairments in these model aneuploids compared to diploid controls that were independent of the cell line and the extra chromosome(s) introduced[6] (**Fig. 1**). Consistent with a defect in HSP90, aneuploid human cells were significantly more sensitive to HSP90 inhibition than cognate diploids. Treatment of aneuploid cells with inhibitors of other protein folding factors or inducers of protein misfolding did not reveal any general sensitivity, indicating that the protein folding defect caused by aneuploidy may indeed be specific for HSP90.

Analysis of the transcriptome and proteome showed consistent downregulation of HSP90 in a panel of aneuploid cells and a more variable reduction in the levels of other molecular chaperones. This prompted us to test whether the levels and activity of HSF1, the master regulator of inducible chaperone expression, were also affected by aneuploidy. Strikingly, we observed consistently lower protein, but not mRNA, levels of HSF1 in aneuploid cells as well as a profound defect in the ability to trigger the HSF1-dependent HSR (**Fig. 1**).

Is the defective HSF1 function in aneuploid cells responsible for their impaired HSP90 activity? To address this question, we constructed cells carrying a third copy of chromosome 8, which carries the *HSF1* gene. We reasoned that the resulting cells, which are aneuploid and have increased expression of HSF1, might be protected against the defect in protein folding engendered by aneuploidy. Indeed, these cells displayed no reduction in HSP90 expression and no apparent defect in HSP90 function as measured using folding sensors and resistance to HSP90

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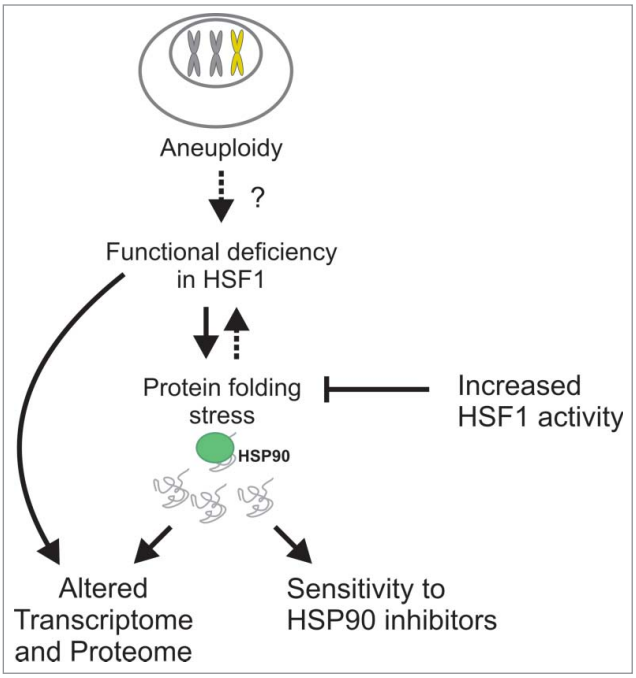

Figure 1. The effects of aneuploidy on protein folding. Aneuploidy impairs the activity of heat shock factor 1 (HSF1) by an as yet undefined mechanism. The reduced function of HSF1 partly determines the transcriptional changes in aneuploid cells and leads to lower expression and activity of HSP90. This in turn leads to lower expression and activity of HSP90-dependent proteins and pathways and sensitivity to HSP90 inhibitors. These effects can be suppressed by increased HSF1 activity.

inhibition. However, one cell line behaved markedly differently; in this clone, which had lost the extra copy of *HSF1*, we observed reduced HSP90 expression and sensitivity to HSP90 inhibition. In further support of a role for HSF1, exogenous overexpression of a constitutively active HSF1 protein rescued the protein-folding defect of aneuploid cells and improved survival in the presence of a HSP90 inhibitor (**Fig. 1**).

Human aneuploid cells exhibit profound genome-wide alterations in both protein and mRNA expression[5,7,8] Intriguingly, the mechanisms underlying these phenomena are not understood. We observed a striking similarity between the transcriptional response to HSF1 knockdown and the transcriptome changes of aneuploid cells. Moreover, the levels of protein clients that strongly interact with HSP90 were lower in aneuploids compared to diploids. Further, we discovered a significant overlap between pathways targeted by HSP90 inhibition and those that are downregulated in aneuploid cells. Taken together, these findings suggest that the altered gene expression observed in aneuploid cells is partly determined by impaired protein folding capacity (**Fig. 1**).

These findings may have two important implications for understanding tumorigenesis. First, by directly linking aneuploidy with impaired protein folding our observations lend strong support to the idea that the proteotoxic stress experienced by tumor cells is at least partly due to aneuploidy. Second, our experiments suggest that the critical requirement for HSF1 in malignant transformation stems partially from its role in protecting against the adverse effects of aneuploidy on protein folding.

Aneuploidy has also been associated with additional stress phenotypes of cancer cells such as metabolic and oxidative stress.[9] Based on these observations, we anticipate that future research may place aneuploidy at the heart of the stress phenotypes of cancer cells. Further, our results suggest that impaired protein folding and its consequences may represent a key pathological feature of diseases such as trisomy syndromes.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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