Yeast DNA damage response pathways and human disease

All living organisms are constantly subjected to a diverse range of environmental genotoxins such as ultraviolet radiation, but even in a perfect environment, DNA damage would be unavoidable; DNA polymerases inevitably make errors, spontaneously stalled replication forks are at high risk to collapse into DNA double strand breaks and free radicals generated during normal cellular metabolism damage thousands of bases per cell per day. DNA damage that is not appropriately repaired leads to accumulating genome instability, which we now know is a major underlying cause of cancer development in humans. Conversely, most contemporary cancer therapies act by causing DNA damage. Interestingly, DNA damage response pathways are highly conserved throughout eukaryotic evolution, and this allows us to use budding yeast as a model to study the principles important for carcinogenesis and cancer therapies in human patients. In yeast and humans, conserved checkpoint proteins including FHA domain-containing kinases Rad53 and Chk2 play crucial roles in delaying the cell cycle in response to DNA damage, to allow for extra time for DNA repair. In addition, these kinases also interact with mRNA poly(A)-tail nucleases to control gene expression after DNA damage at the post-transcriptional level, and via their FHA domains they bind conserved DNA repair proteins. Surprisingly, Rad53 via its conserved FHA domain also appears to be involved in regulating filamentous differentiation in pathogenic fungi, indicating that the analyses of yeast checkpoint responses may be of direct benefit for public health.

Human Chk2 mutations cause the rare Li-Fraumeni syndrome where patients suffer from multiple independent cancers throughout their lifetime. Chk2-like kinases are characterised by the presence of an N-terminal FHA domain that functions to link these kinases to upstream activators as well as downstream targets. Yeast contains two mitotic checkpoint kinases, Rad53 and Chk2, and they share a similar domain topology (Figure 1), with zinc-finger or RNA recognition motif (RRM) domains as potential nucleic acid binding regions near the N-terminus and an SQ/TQ cluster domain (SCD) near the C-terminus. SCDs are dense phosphorylation site regions for upstream kinases. Rad53 via its conserved FHA domain also appears to be involved in regulating filamentous differentiation in pathogenic fungi, indicating that the analyses of yeast checkpoint responses may be of direct benefit for public health.

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We have also identified two novel DNA damage response proteins, yeast Mdt1 and human ASCIZ, as ligands for the N-terminal FHA domains of Rad53 and Chk2, respectively. Interestingly, these two proteins share a similar degree of sequence similarity (36% strongly conserved residue) as Rad53 and Chk2, and they share a similar domain topology (Figure 2), with zinc-finger or RNA recognition motif (RRM) domains as potential nucleic acid binding regions near the N-terminus and an SQ/TQ cluster domain (SCD) near the C-terminus. SCDs are dense phosphorylation site regions for the most upstream DNA damage kinases Mec1/Tel1 in yeast and ATM/ATR in humans, and are now considered to be a structural hallmark of DNA damage response proteins including Chk2 and Rad53 (Figure 1). Furthermore, ASCIZ and Mdt1 both seem to have roles in lesion-specific DNA recombination pathways, as has also been shown in our unpublished research.
In addition to a range of DNA damage-related phenotypes, yeast mdt1\textsuperscript{D} mutants also have an unusual, elongated cell shape\textsuperscript{6}. In this regard, it is interesting that a number of additional ligands for the N-terminal Rad53 FHA domain in budding yeast were recently identified as also seeming to regulate polarised cell growth\textsuperscript{9}. Remarkably, this function of the Rad53 FHA\textsubscript{1} domain in cell morphogenesis seems to be conserved in the pathogenic fungus \textit{Candida albicans}, where it regulates the switch from the yeast form to the clinically more virulent hyphal growth form in response to genomic stress\textsuperscript{10}. This surprising link between the experimental analysis of Rad53 as a model for human cancer biology and its direct relevance as a virulence factor for infectious diseases represents just another exciting example of how new therapeutic targets can emerge unexpectedly from seemingly unrelated curiosity-driven basic biomedical research.

**Acknowledgements**

I thank Ana Traven for comments on the manuscript. My laboratory is funded by the National Health and Medical Research Council of Australia and the Cancer Council Victoria.

**References**


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