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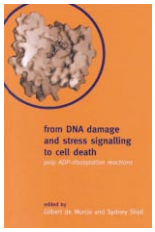

From DNA Damage and Stress Signalling to Cell Death

by Gilbert de Murcia and Sydney Shall, Oxford University Press, 2000, 238 pages, hardback, £70.00, ISBN: 0 19 850633 3

Until death do us PARP

This book provides a comprehensive review of the technically difficult and rapidly evolving scientific area of poly ADP-ribosylation. The phenomenon of ADP-ribosylation and its role in chromatin organization has been around for a considerable length of time but it is only recently that major advances have been made in understanding the role of this process during DNA damage and stress signaling leading to death of the cell.

The book begins with an extremely useful list of abbreviations, which is a vital reference to the reader considering the complexity of this area and a tool that can be referred to continuously throughout the book. The first chapter provides a good general introduction to ADP-ribosylation and the major players involved in this process and speculates as to the interplay between cellular energy metabolism and cellular signaling. The area covering the discovery aspects could have been shorter and can be skipped as it is not essential for the understanding of this area to readers whose interest in ADP-ribosylation is not central to their research. At this point, it would have been more useful to briefly speculate on the potential role of PARP [poly (ADP-ribose) polymerase] in chromatin structure and gene regulation, as this was not discussed until later (page 54 and into Chapter 3) in the book.

Chapter 4 (Affar *et al.*) provides a good thorough review of the role of PARP in cell death, raising valuable discussion points and a particularly interesting section summarizing the knockout studies with PARP. *In vitro* studies with tissues/cells from these animals provide compelling evidence for a crucial role for this enzyme in apoptosis.

The suicide hypothesis presented in Chapter 5 raises discussion around the fact that high levels of DNA damage result in necrosis (by energy depletion) and not apoptosis. The PARP inhibitor INH2BP is first mentioned well into the book (page 163), which begs the question as to whether this compound should be used more extensively to understand the function of PARP in the various *in vitro* and *in vivo* assays available. It is clear from Chapter 6, which covers the development of inhibitors of PARP, that potent small-molecule selective inhibitors are required against PARP to tease out the relative contributions of these different pathways to necrosis/apoptosis/energy depletion. The role of poly ADP-ribosylation in apoptosis needs to be examined more thoroughly. The availability of inhibitors of some of the other players in the apoptosis cascade (such as the caspases) could provide evidence for the crucial role of ribosylation during programmed cell death. It appears that cell- and signal-specific apoptosis will become increasingly important as potential novel therapeutic targets to treat diseases in which there is dysregulated apoptosis and a thorough understanding of the role of PARP in these specific pathways will probably be required in the future.

Importantly, there is increasing evidence that chromatin scaffolding/structure plays a central role in gene regulation. Ribosylation of discrete regions of transcriptionally active DNA could provide a means to control or amplify gene expression in response to stress influences. The availability of the total genome sequence could enable identification of 'hot-spots' of ADP-ribosylation, and could provide clues to a higher-order control of this fundamental cellular process in gene regulation.

An excellent closing perspectives chapter is provided by Sydney Shall, which summarizes the evidence provided but, importantly, speculates as to the way forward in further understanding how ADP-ribosylation could play such a crucial role in the response of cells to death inducers and also its role in normal physiology as a guardian of the genome.

In summary, this is an excellent book for researchers who would like not only a comprehensive introduction to this area but also clues as to how to proceed in trying to clarify the interplay between energy metabolism, intracellular signaling and cell death.

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