At the same time, a number of aspects of the biology of PARPs and related proteins remain to be explored. For example, we still know very little about the broad spectrum of biology dependent on the PARP family of proteins. In addition, our understanding of the different catalytic-dependent and catalytic-independent functions of PARPs is limited. Furthermore, while numerous examples of ADP-ribose "reader" domains exist in nature, a comprehensive understanding of the functions of the proteins that contain these domains has been elusive.

With respect to ADP-ribosylation, the factors that drive selectivity and specificity for different substrates by different PARPs have been incompletely elucidated. Additionally, determining the repertoire of targets of distinct PARPs and their sites of ADP-ribosylation in different tissues is in its infancy. Likewise, the broader spectrum of amino acids that function as acceptors of ADP-ribose is still being defined (e.g., serine and cysteine) (Leidecker et al. 2016; Westcott et al. 2017). Such information would provide new insights into the biological roles of PARP across tissues and in disease states. One of the greatest needs and most significant challenges in the field, however, is moving beyond the identification of sites of ADP-ribosylation toward the determination of the functional relevance of ADP-ribosylation at those sites, which will reveal the definitive biological consequences of ADP-ribosylation. Finally, the field has not fully explored the therapeutic potential of PARPis. In conclusion, even after five decades of research on PARPs and ADP-ribosylation, much work remains to be done.

Competing interest statement

W.L.K. is a founder and consultant for Ribon Therapeutics, Inc.

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