

Preface

ADP-ribosylation was originally discovered as a posttranslational protein modification catalyzed by Diphtheria Toxin (DT) and Cholera Toxin (CT). These toxins are secreted by *Corynebacterium diphtheriae* and *Vibrio cholera* as a multidomain protein (DT) or as a binary AB₅ protein complex (CT). Each of these toxins harbors a catalytic ADP-ribosyltransferase (ART) domain. Structurally, the enzymatic domains of DT and CT are related, even though they show very limited sequence similarity. Following translocation across cellular membranes to the cytosol of mammalian cells, the ART domains of these toxins transfer ADP-ribose from NAD⁺ to a specific amino acid in a specific target protein; in case of DT to Diphthamide 687 (a modified histidine residue) of elongation factor 2, in case of CT to Arginine 187 in the alpha subunit of heterotrimeric G proteins. Due to their high specificity, these toxins are still widely used today as tools to delete specific cell types (DT) or to study signaling via G-protein coupled receptors (CT).

Molecular cloning and 3D-structure analyses have uncovered endogenous enzymes related to DT and CT in many organisms from all kingdoms of life. Remarkably, these endogenous ARTs fall into two major subclasses that are distinguished by conserved structural motifs: H-Y-E in the ARTD subfamily (related to Diphtheria Toxin), R-S-E in the ARTC subfamily (related to C2 and C3 Clostridial Toxins).

Biochemical analyses have uncovered ARTs that ADP-ribosylate amino acids other than diphthamide and arginine, the targets of DT and CT. These include cysteine, asparagine, threonine, glutamine, lysine, and glutamate. Moreover, structurally related ARTs have been discovered that ADP-ribosylate nucleotides or antibiotics. ADP-ribosylation is a potentially reversible modification. Two distinct enzyme families are known that catalyze de-ADP-ribosylation of ADP-ribosylated proteins. These include ADP-ribosylhydrolases (ARHs) and macro-domain/poly-ADP-ribosylglycohydrolases (PARGs).

Database and structural analyses indicate that endogenous ARTs, ARHs, and PARGs in plants and animals have been acquired by lateral gene transfer from procaryotes. Indeed, as laid out in the chapter by L. Aravind, the origin of these enzymes seems to lie in polymorphic prokaryotic biological conflict systems.

This volume brings together ten papers from renowned experts in the field that review exciting recent findings on ADP-ribosylation. This field is important not only because it delivers a better understanding of ADP-ribosylating toxins and their endogenous relatives, but also because this understanding provides a basis for developing toxin-neutralizing drugs and drugs that target endogenous ART relatives. I am confident that the reader will enjoy the interesting contributions in this special issue on endogenous ADP-ribosylation.

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