Published in final edited form as:

Nat Rev Drug Discov. 2019 October ; 18(11): 815. doi:10.1038/d41573-019-00158-w.

ADCK3/COQ8A: the choice target of the UbiB protein kinase-like family

Christopher R. M. Asquith^{1,*}, Nathan H. Murray^{2,3}, David J. Pagliarini^{2,3,*}

¹Department of Pharmacology, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

²Morgridge Institute for Research, Madison, WI, USA

³Department of Biochemistry, University of Wisconsin-Madison, Madison, WI, USA

UbiB kinase-like proteins exist in archaea, bacteria and eukaryotes, and comprise ~25% of all microbial protein kinase-like (PKL) enzymes. The founding member of the UbiB family, UbiB from *Escherichia coli*, supports the biosynthesis of ubiquinone, also known as coenzyme Q (CoQ), by an unknown mechanism. In eukaryotes, UbiB homologues are found exclusively in mitochondria, where they likewise have been connected to CoQ biosynthesis (for a review, see *Trends Biochem. Sci.* **42**, 824–843; 2017).

Mutations in two of the five human UbiB homologues, COQ8A (ADCK3) and COQ8B (ADCK4), give rise to neurological and kidney disorders, respectively, both associated with CoQ deficiency. To date, only UbiB, its *Saccharomyces cerevisiae* orthologue Coq8p and COQ8A (collectively referred to here as COQ8) have been studied in depth biochemically, and COQ8A is therefore the focus of this article.

Biological functions.

COQ8 was originally speculated to be a protein kinase. However, subsequent structural work revealed that the COQ8 active site is sterically occluded by UbiB-specific domains, suggesting that it possesses unorthodox functionality in lieu of typical protein kinase activity (*Mol. Cell* **57**, 83–94; 2015). COQ8 possesses a conserved ATPase activity that is activated by binding to membranes containing cardiolipin and by phenolic compounds that resemble CoQ pathway intermediates (*Cell Chem. Biol.* **25**, 154–165; 2018). This ATPase activity appears to be essential for COQ8's role in CoQ biosynthesis, where it supports the integrity of a biosynthetic complex of other CoQ-related proteins. Although its precise mechanism of action remains unclear, a current model proposes that COQ8 leverages its ATPase activity to access hydrophobic CoQ intermediates within the mitochondrial inner membrane (FIG. 1a).

* chris.asquith@unc.edu; dpagliarini@morgridge.org.

Competing interests

The authors declare no competing interests.

RELATED LINKS

Dark Kinase Knowledgebase (COQ8A): <https://darkkinome.org/kinase/COQ8A>

Pharos (COQ8A): <https://pharos.nih.gov/targets/COQ8A>

Chemical tools.

A chemical genetic knockout system in *S. cerevisiae* was established to probe COQ8 function. Two point mutations to cysteines in Coq8p enable it to accept a halomethyl ketone compound, which irreversibly inhibits the protein (*Cell Chem. Biol.* **25**, 154–165; 2018).

However, literature tool compounds for the human protein, COQ8A, are sparse. Several very promiscuous compounds show reasonable biochemical potency, including dasatinib (dissociation constant (K_d) = 190 nM), PD-173955 (K_d = 910 nM) and R406 (K_d = 1100 nM), with only TG-100-115 (K_d = 94 nM) below 100 nM (*Nat. Biotechnol.* **29**, 1046–1051; 2011). Owing to their promiscuity, these compounds are of very limited use for establishing a phenotype for COQ8A inhibition, although they could be starting points for medicinal chemistry efforts.

Recently, a chemical probe developed for cyclin G-associated kinase (GAK) known as SGC-GAK-1 showed COQ8A as an off-target (GAK K_d = 1.9 nM and COQ8A K_d = 190 nM) (*J. Med. Chem.* **62**, 2830–2836; 2019). A quinoline analogue of this series (UNC-CA157) (FIG. 1b) demonstrated the most potent COQ8A binding for a small-molecule inhibitor in the literature to our knowledge (K_d = 66 nM) to date. This series more generally has also been shown to have a narrow-spectrum kinome inhibition profile (*ChemMedChem* **13**, 48–66; 2018). The literature therefore provides a potential foundation to inform the design of a selective cell-active COQ8A inhibitor through combining information from multiple chemotypes.

Acknowledgements

This article is part of a series from the NIH Common Fund Illuminating the Druggable Genome (IDG) programme. The goal of IDG is to catalyse research on understudied proteins from druggable gene families by providing reagents, phenotypes and a mineable database, focusing on G protein-coupled receptors, kinases and ion channels. For more information, see <https://druggablegenome.net/>. Work was also supported by NIH R35GM131795 (D.J.P.) and NIH T32GM008505/NSF DGE-1747503 (N.H.M.).

Fig. 1 |. COQ8A function and modulation.

a | Model of COQ8A facilitating CoQ biosynthesis through its ATPase activity. COQ8A may use this activity to gain access to hydrophobic CoQ intermediates and deliver mature CoQ into the hydrophobic region of the mitochondrial inner membrane. The domain structure of COQ8A, as described in *Mol. Cell* **57**, 83–94; 2015, is highlighted and other proteins involved in CoQ biosynthesis are indicated as circles. The structures of CoQ and its precursor have been simplified for clarity; for details, see *Trends Biochem. Sci.* **42**, 824–843; 2017. **b** | Structure of the quinoline analogue UNC-CA157 with reported kinase inhibition values. GAK, G-associated kinase; NLK, Nemo-like kinase; P_i, inorganic phosphate; RIPK2, receptor-interacting serine/threonine protein kinase 2.