The Role of POPDC1 in the Progression of the Malignant Phenotype

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Abstract

The Popeye Domain Containing Protein 1 (POPDC1), a tight junction-associated transmembrane protein with a unique binding site for cAMP, has been shown to act as a tumour suppressor in cancer cells. Through interaction with many downstream effectors and signalling pathways, POPDC1 promotes cell adhesion and inhibits uncontrolled cell proliferation, epithelial-to-mesenchymal transition, and metastasis. However, POPDC1 expression is downregulated in many types of cancer, thereby reducing its tumour-suppressive actions. This review discusses the role of POPDC1 in the progression of the malignant phenotype and highlights the broad range of benefits POPDC1 stabilisation may achieve therapeutically. Cancer stem cells (CSC) are a key hallmark of malignancies and commonly promote treatment resistance. This article provides a comprehensive overview of CSC signalling mechanisms, many of which have been shown to be regulated by POPDC1 in other cell types, thus suggesting an additional therapeutic benefit for POPDC1-stabilising anticancer drugs.

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	POPDC2	POPDC3	Reference
Cardiovascular Disease	Under-expressed causing decreased conduction and AV block in cardiac muscle only. Associated with W188X mutation.	-	Brand, 2019 Amunjela *et al.*, 2019
Limb Girdle Muscular Dystrophy (LGMD)	-	Mutant (L155H, L217F, R261Q) POPDC3 expression leads to skeletal muscular dystrophy.	Vissing *et al.*, 2019
Ductal Breast Carcinoma (especially HER2+ subtype)	Over-expressed at all clinical stages. Possibly implicated in cancer initiation and sustenance.	Over-expressed at early clinical stages.	Amunjela and Tucker, 2017a
Head and Neck Squamous Cell Carcinoma (HNSCC)	-	Over-expression correlates with low patient survival. Potential biomarker for radio therapy resistance.	He *et al.*, 2019
Gastric Cancer	-	Under-expression due to promoter hypermethylation. Lower POPDC3 levels correlate with increased depth of invasion and metastasis.	Lue *et al.*, 2012 Kim *et al.*, 2010
Oesophageal and Lung Cancer	-	Overexpression of POPDC3 correlates with greater radiotherapy resistance.	He *et al.*, 2019

Table 1 - The Role of POPDC2 and POPDC3 in Disease

Expression of POPDC2 and POPDC3 varies between tissue type and across various cancer types. Dysregulation of POPDC2 is mainly observed in cardiovascular disease and breast cancer. POPDC3 mutations are implicated in limb girdle muscular dystrophy and has been shown to have both tumour-suppressive and oncogenic roles in different malignancies.

Protein	Interacting Sequence of POPDC1	Tissue location of POPDC1 interaction	Suggested Role	References
TREK-1	Unknown sequence on CTD	Cardiac myocytes	Interaction with POPDC1 enhances current flow in cardiac myocytes	Han *et al.*, 2019 Brand, 2019
CAV-3	aa242-266	Skeletal muscle sarcolemma, cardiac myocyte transverse tubules	POPDC1 ensures structural integrity and function of Cav-3	Han *et al.*, 2019 Brand, 2019
VAMP3	CTD sequence after aa118	MDCK cells, adult cardiac and skeletal muscle	POPDC1 interaction ensures adequate recycling of β1-integrins. Loss of this interaction increases migration.	Hager *et al.*, 2010
GEFT	aa250-300	Human Corneal Epithelia, Murine NIH T3T Cells	Retention of GEFT in membrane, preventing Rac1/Cdc42/RhoA activation promoting TJ formation	Russ *et al.*, 2010, Smith *et al.*, 2008
GEFH	Unknown sequence on CTD	Human Corneal Epithelia	POPDC1 sequesters GEFH to cell membrane to prevent RhoA signalling	Russ *et al.*, 2011, Parang *et al.*, 2018
ZO-1	Unknown sequence on CTD	Trabecular meshwork cells, HCE, uveal melanoma	POPDC1/ZO-1 interaction prevents ZONAB-induced entry to cell cycle and translation of proliferative genes	Russ *et al.*, 2010, Russ *et al.*, 2011 Amunjela *et al.*, 2019, Jayagopal *et al.*, 2011
Occludin	Unknown sequence on CTD	HCE, uveal melanoma	Maintenance of tight junction formation	
Bnip3	Unknown sequence on CTD	Cardiac Myocytes	POPDC1 suppresses Bnip3-induced apoptosis	Kliminski *et al.*, 2016
LRP6 (Wnt/β-catenin-pathway)	Unknown sequence on CTD	HEK293 cells, human colonoids, murine adenoma tumoroids	Prevention of β-catenin activation by inhibition of LRP6	Thompson *et al.*, 2019
PR61α (c-Myc pathway)	aa330-345	Murine colitis-associated cancer cells	Promotes c-Myc ubiquitination / degradation	Parang *et al.*, 2017

Table 2 – POPDC1 Downstream Targets

The POPDC1 protein interacts with many downstream including TREK1, CAV-3, VAMP3, GEFT, GEFH, ZO-1, occludin, Bnip3, LRP6 and PR61α. This interaction has mainly been shown in cardiac and skeletal muscle cells, however, an increasing body of evidence is emerging that demonstrates POPDC1 interaction with these targets in cancer cells.

Abbreviations: CTD (C-terminal domain), HCE (human corneal epithelial cells), HEK293 (human embryonic kidney cells)

Mechanisms of POPDC1 Downregulation	Cancer type	Reference
Promoter Hypermethylation	CRC, PC, BC, NSCLC, Glioma, HNSCC, GC	Williams *et al*., 2010; Parang *et al*., 2017, Amunjela and Tucker, 2016; Kim *et al*., 2010.
Under-expression of miRNA-122	HCC	Wang *et al*., 2014
Over-expression of Netrin-1	HCC	Han *et al*., 2015
EGFR activation	BC	Amunjela and Tucker, 2017a

Table 3 – Mechanisms of POPDC1 Downregulation Associated with Various Cancer Types

The four main mechanisms of PODPC1 downregulation include promoter hypermethylation, under-expression of miRNA-122 reducing POPDC1 gene transcription, over-expression of netrin-1 leading to inhibited POPDC1 expression and EGFR activation, which phosphorylates and inactivates POPDC1. These mechanisms have been observed in many different cancer types including HCC, CRC, BC, PC, NSCLC, HNSCC and glioma. The most commonly identified mechanism of POPDC1 downregulation is promoter hypermethylation.

***Abbreviations*:** CRC (colorectal cancer), PC (prostate cancer), BC (breast cancer), NSCLC (non-small cell lung cancer), HNSCC (head and neck squamous cell carcinoma), GC (gastric cancer), HCC (hepatocellular carcinoma).

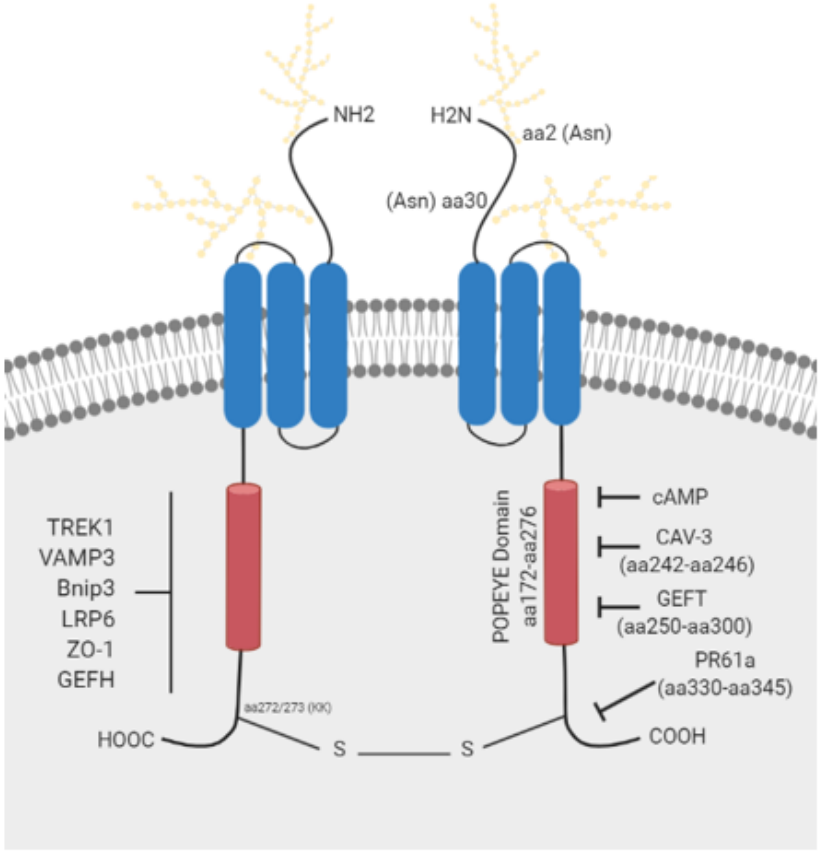

Figure 1 – The Structure of Popeye Domain Containing Protein 1 (POPDC1)

POPDC1 is a transmembrane protein highly expressed in cardiac myocytes, skeletal muscle and some cancer cells. The short extracellular N-terminal domain contains two glycosylation sites (asparagine residues at positions aa2 and aa30). This is followed by three membrane-spanning domains and a long intracellular C-terminal domain (CTD). The CTD contains the highly conserved POPEYE domain (aa172-aa276) with a unique cAMP binding site. Other binding sites exist for TREK1, VAMP3, Bnip3, LRP6, ZO-1, GEFH, CAV-3 (aa242-246), GEFT (aa250-300) and PR61α (aa330-aa345). A disulfide bridge forms between intracellular cysteine residues with lysine residues (aa272/273) critically required for this dimerisation, which promotes membrane stabilisation.

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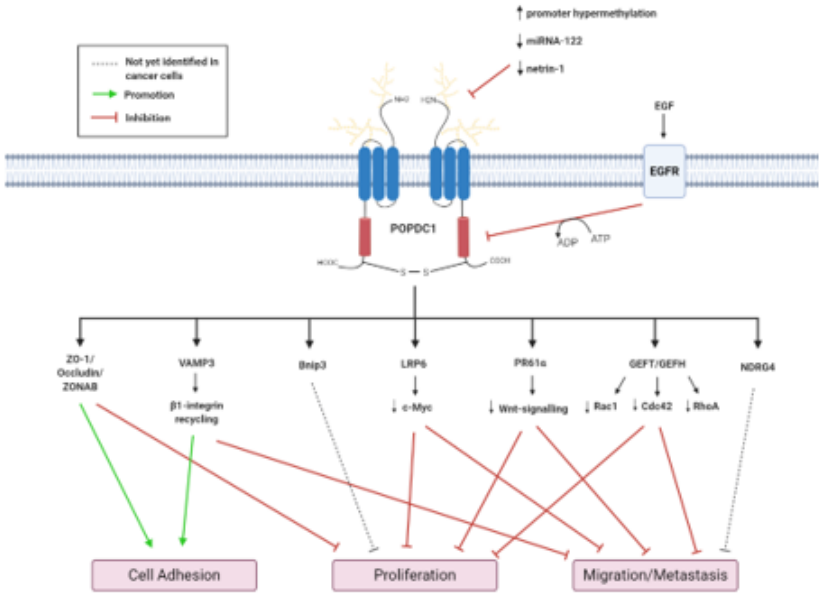

Figure 2 - Regulatory Roles of POPDC1 in Cancer

POPDC1 acts as a tumour suppressor by influencing three main processes involved in cancer progression. Its interaction with tight junction-associated proteins (e.g. ZO-1, occludin, ZONAB) and VAMP3 ensures maintenance of cell adhesion. Furthermore, POPDC1 inhibits uncontrolled cell proliferation through its interactions with guanine nucleotide exchange factors (GEFT/GEFH) and the c-Myc and Wnt-signalling pathways. POPDC1 also plays an important role in suppressing cancer cell migration and metastasis.

Loss of these regulatory roles exerted by POPDC1 can occur as a result of intracellular phosphorylation (through EGFR) or reduced gene expression due to promoter hypermethylation, reduced miRNA-122 expression or increases netrin-1 activity.

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