The Popeye Domain Containing Gene Family

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The Popeye domain containing (POPDC) genes encode a novel class of 3',5'-cyclic adenosine monophosphate (cAMP) effector proteins, which are localized to the plasma membrane. Mutations of POPDC genes have been associated with cardiac and skeletal muscle disease. However POPDC genes also play a role as tumor suppressor by interacting with proteins involved in cell migration, cell signaling and cell cycle control.

Keywords: Popeye domain containing (POPDC) ; striated muscle ; cAMP ; tumor suppressor ; arrhythmia

1. Introdution

The Popeye domain containing (POPDC) gene family consists of *POPDC1* (also known as *BVES)*, *POPDC2* and *POPDC3* and encodes a novel class of 3',5'-cyclic adenosine monophosphate (cAMP) effector proteins. Despite first reports of their isolation and initial characterization at the protein level dating back 20 years, only recently major advances in defining their biological functions and disease association have been made. Loss-of-function experiments in mice and zebrafish established an important role in skeletal muscle regeneration, heart rhythm control and stress signaling. Patients suffering from muscular dystrophy and atrioventricular block were found to carry missense and nonsense mutations in either of the three POPDC genes, which suggests an important function in the control of striated muscle homeostasis. However, POPDC genes are also expressed in a number of epithelial cells and function as tumor suppressor genes involved in the control of epithelial structure, tight junction formation and signaling. Suppression of *POPDC* genes enhances tumor cell proliferation, migration, invasion and metastasis in a variety of human cancers, thus promoting a malignant phenotype. Moreover, downregulation of *POPDC1* and *POPDC3* expression in different cancer types has been associated with poor prognosis. However, high *POPDC3* expression has also been correlated to poor clinical prognosis in head and neck squamous cell carcinoma, suggesting that *POPDC3* potentially plays different roles in the progression of different types of cancer. Interestingly, a gain of *POPDC1* function in tumor cells inhibits cell proliferation, migration and invasion thereby reducing malignancy. Furthermore, POPDC proteins have been implicated in the control of cell cycle genes and epidermal growth factor and Wnt signaling. Work in tumor cell lines suggest that cyclic nucleotide binding may also be important in epithelial cells. Thus, POPDC proteins have a prominent role in tissue homeostasis and cellular signaling in both epithelia and striated muscle.

2. The Role of POPDC Proteins in Striated Muscle

POPDC genes are expressed at high levels in the heart and skeletal muscle [1]. While *Popdc1* is expressed at nearly equal levels in both types of striated muscle, *Popdc2* is strongly expressed in the heart and only weakly in skeletal muscle, while the reverse is true for *Popdc3* [2]. In order to gain insight into the function of POPDC genes, null mutations for *Popdc1* and *Popdc2* were generated in mice [3][4]. Homozygous null mutants for both genes are viable and do not display any overt pathology other than lower heart and body weights and an elevated blood pressure [5]. The expression level of *Popdc1* and *Popdc2* in the cardiac conduction system is higher than in the working myocardium. Likewise, the sinoatrial (SAN) and atrioventricular nodes (AVN) show a prominent expression of both genes [3]. In order to test whether the null mutants display a cardiac arrhythmia phenotype, telemetric ECG devices were implanted into mutant and control mice and heart rate and ECG pattern were monitored. Both *Popdc1* and *Popdc2* KO mice develop a stress-induced bradycardia in an age-dependent manner [3]. The bradycardia phenotype is associated with some morphological aberrations such as a loss of cell extensions normally present in pacemaker myocytes [6] and a loss of pacemaker myocytes in the tail region of the SAN [3]. Whether these aberrant morphologies have any functional consequences is, however, presently unknown. Cardiac arrhythmia is also observed in zebrafish *popdc1* and *popdc2* morphants and the *popdc1* null mutant [7][8]. However, in contrast to the sinus bradycardia present in mutant mice, an AV-block is seen in zebrafish.

Recently, mutations in *POPDC1*, *POPDC2* and *POPDC3* have been discovered in patients that suffer from heart and skeletal muscle disease (**Table 1**). In the case of *POPDC1*, patients that carry mutations develop limb-girdle muscular dystrophy (LGMD) and an atrioventricular (AV)-block of varying degree [7][9]. In contrast, patients carrying a *POPDC2* mutation develop a severe third-degree AV-block, but skeletal muscle appears to be unaffected [10]. The reverse is true for *POPDC3*, as in this case only skeletal muscle is affected and patients develop a severe LGMD, but the heart is normal [11]. The differential effect of POPDC mutations on heart and skeletal muscle maybe related to the expression level of each isoform, or alternatively that the different isoforms have unique functions, specific to cardiac or skeletal muscle, respectively.

Table 1. Cardiac and skeletal muscle phenotypes in model organism and patients.

Species	Mutation	Heart	Skeletal Muscle	References
mouse	***Popdc1*$^{-/-}$**	**stress-induced sinus bradycardia**	**regeneration defect**	[3][4]
		ischemia-reperfusion damage		[5]
	***Popdc2*$^{-/-}$**	**stress-induced sinus bradycardia**	**no phenotype reported**	[3]
zebrafish	***popdc1* morphants**	**AV-block, pericardial effusion**	**muscular dystrophy**	[7]
	***popdc2* morphants**	**AV-block, pericardial effusion**	**muscular dystrophy**	[8]
	***popdc1*^{S191F}**	**AV-block, pericardial effusion**	**muscular dystrophy**	[7]
human	***POPDC1***			
	p.S201F	**2nd degree AV-block**	**LGMDR25**	[7]
	c.1A > G	**1st degree AV-block**	**LGMDR25**	[9]
	p.V217-L272del	**1st/2nd degree heart block**	**LGMDR25**	[9]
	p.R88X	**1st degree AV-block**	**LGMDR25**	[9]
	POPDC2			
	p.W188X	**3rd degree AV-block**	**no muscle phenotype**	[10]
	POPDC3			
	p.L155H	**no cardiac phenotype**	**LGMD**	[11]
	p.L217F	**no cardiac phenotype**	**LGMD**	[11]
	p.R261Q	**no cardiac phenotype**	**LGMD**	[11]

In patients carrying *POPDC1* mutations, the expression and subcellular localization of POPDC1 and POPDC2 was studied in skeletal muscle biopsies. Interestingly, membrane localization of the mutant POPDC1 protein was severely compromised and a massive loss of the mutant protein was observed [7][9]. In the case of patients carrying the *POPDC1*^{S201F} mutation, a perinuclear expression domain of the mutant protein has been described [7]. For some of the mutations, a reduction in *POPDC1* mRNA through nonsense-mediated decay (NMD) was demonstrated [9]. Unexpectedly, in addition to the aberrant cytosolic localization of POPDC1, the expression of POPDC2 was also significantly impaired. A strongly reduced cytosolic localization of POPDC2 was observed in all patients carrying missense or nonsense mutations of *POPDC1* [7][9]. Interestingly, while *POPDC3* mutations have also been linked to LGMD, the biopsies of patients carrying any one of the three identified POPDC3 mutations do not display aberrant membrane localization of the mutant protein, nor were there any alterations observed in POPDC1 or POPDC2 [11] suggesting that differences exist between the pathogenic processes that are trigged by different POPDC isoforms.

A defect in skeletal muscle structure and function in animal models has so far been best documented in the case of *popdc1* and *popdc2* morphants in zebrafish, which display an aberrant structure of the facial and tail musculature [7][8]. A common feature of the phenotype in both morphants and mutants is the aberrant structure of the myotendinous junction (MTJ), which is a specialized basement membrane and required to transmit force between tendon and muscle [12]. Electron microscopy of the *popdc1* mutants revealed a lack of the electron dense matrix proteins (mainly a network of collagen type, I, III and IV), which accumulates in the MTJ [7]. As a putative consequence of the impaired MTJ development, myofiber detachment was observed in *popdc1*, *popdc2* and, although rare, also in *popdc3* morphants [7][11] [8]. The common phenotype seen in case of *popdc1–3* morphants suggests an important role of POPDC proteins in MTJ

formation. Since POPDC1 has been demonstrated to interact with dystrophin, which has an important role in MTJ formation in zebrafish, it could potentially define a molecular pathway that is affected by the loss of POPDC protein function [7].

Interestingly, patients carrying *POPDC1* and *POPDC3* mutations display elevated to high CK levels, which suggest compromised sarcolemmal integrity. Minor defects of the plasma membrane are repaired via a mechanism that involves a large number of proteins including dysferlin [13], which was recently identified as an POPDC1-interacting protein [7]. Skeletal muscle fibers of the oldest patient carrying the homozygous POPDC1^{S201F} mutation display focal damage of the sarcolemma, which suggests that impaired sarcolemmal repair may be a feature of carriers of *POPDC1* mutations [7]. Presently it is unclear how POPDC proteins might be involved in membrane repair, which is known to be triggered by elevated cytosolic Ca^{2+}-levels. However, Ca^{2+}-influx may trigger cAMP production via the activation of a Ca^{2+}-inducible AC isoform. Increases in cAMP have been implicated in membrane repair response in the case of some cell types but has not been studied in relation to sarcolemmal repair in striated muscle [14].

Severe muscle injuries involve the activation of satellite cells, a stem cell population, which is located adjacent to the muscle fiber and shares the same basement membrane [15]. Activated satellite cells proliferate in response to injury, fuse to form myotubes, differentiate and increase in size by hypertrophy. Ultimately the newly regenerated muscle fibers are able to substitute the damaged ones and fully restore the contractile function of the injured muscle. Injury of hindlimb muscles of *Popdc1* null mutant mice was experimentally induced by cardiotoxin injection, which triggers Ca^{2+}-overload and fiber necrosis [4]. In the *Popdc1* null mutant muscle, regeneration is retarded compared to wildtype mice and newly formed muscle fibers were much smaller in the mutant muscle. The molecular basis for the impaired regenerative response is poorly understood. However, in activated satellite cells, POPDC1 is located in the nucleoplasm, while myotube formation triggers a loss of nuclear localization [16]. It will be interesting to find out whether nuclear function of POPDC proteins involves transcriptional control, given that the bacterial CAP and CRP proteins are the closest related proteins. POPDC proteins apparently have multiple modes to maintain homeostasis in striated muscle.

3. The Roles of POPDC Proteins in Cell Migration, Invasion and Metastasis

Consistent with POPDC1 being a tumor suppressor, the loss of POPDC1 has been shown to promote cell migration, invasion and metastasis in various cancer types [17][18][19][20][21]. Indeed, POPDC1 inhibits cell migration and invasion in hepatocellular carcinoma [18] and colorectal cancer cells [22]. The gain of POPDC1 function also inhibits tumor growth and metastasis of colorectal carcinoma cells [22]. The mechanism by which POPDC1 regulates cell migration, invasion and metastasis can be partly linked to its role in the maintenance of adherence and tight junctions. The loss of cell–cell contact at the tight junctions can lead to the detachment of cells from the primary tumor enabling cells to more easily migrate and invade adjacent tissue or breach the basement [23][24]. These processes represent the initial steps of metastasis that occur prior to the intravasation of tumor cells into blood or lymphatic circulation [23]. The mechanism by which POPDC1 regulates cell migration, invasion and metastasis could therefore be partly linked to its role in the maintenance of adherence and tight junctions.

In vitro experiments using corneal epithelial cells demonstrated enhanced localization of POPDC1 at the cell membrane and adherence junctions in response to cell–cell contact [25][26]. However, in migratory epithelial cells surface expression of POPDC1 was reduced [26]. In addition, the suppression of POPDC1 with the help of antisense morpholino in corneal epithelial cells also resulted in the disruption of epithelial integrity and enhanced cell migration [26]. This is consistent with high POPDC1 expression being required for adhesion maintenance by interacting with tight junction molecules such as ZO-1 [25]. Further support for this hypothesis comes from the fact that high POPDC1 levels reappeared at the epithelial surface when cells ceased to migrate and initiated cell–cell contact [26]. These findings highlight the fact that reduced expression of POPDC1 at the cell surface is favorable to ensure cell migration. In addition, this data corroborates findings in non-adhesive fibroblastic L-cells where the overexpression of POPDC1 in these cells induced adhesive behavior [25][27] suggesting that high POPDC1 expression inhibits cell migration by promoting cell adhesion.

This gives further support to the hypothesis that POPDC1 is a tumor suppressor whose high expression and function inhibits malignant behavior such as the initiation of cell migration, while its loss of function promotes a migratory and malignant phenotype in tumor cells. Interestingly, the suppression of POPDC1 has been shown to promote cell migration and invasiveness of breast cancer cells [17][19], gastric cancer cells [28][20], and hepatocellular carcinoma cells [18][21]. Furthermore, suppression of POPDC1 has been correlated to enhanced metastasis and poor clinical outcomes in gastric cancer [20]. Since loss of adhesion (cell detachment), cell migration and invasion are events that promote metastasis [23] [24], the role of POPDC1 in preventing metastasis could be linked to its functions in regulating cell-adhesion.

Although the effects of POPDC2 and POPDC3 on cell migration, invasion and metastasis have not been extensively studied, the suppression of POPDC3 has been shown to stimulate cell migration and invasion in gastric carcinoma cells [20]. In addition, low POPDC3 expression has also been correlated to metastasis and high depth of invasion in gastric cancer [20]. This suggest that POPDC3 potentially regulates cell migration, invasion and metastasis. It is, however, unclear whether POPDC3 regulates these processes via a similar mechanism or potential interaction partners such as POPDC1. Further studies are thus required to elucidate the mechanisms by which POPDC1 and POPDC3 proteins promote cell migration, invasion and metastasis. It would also be interesting to determine if POPDC1 regulates migration via other additional mechanisms or if it interacts with other molecules in addition to ZO-1, that regulate cell adhesion.

POPDC1 has also been shown to interact with molecules in pathways that regulate cell migration such as GEFT, NDRG4 and Netrin-1 [18][29][30]. Hence the effects of POPDC1 on cell migration can potentially also be mediated via its interaction with molecules in these pathways. N-Myc downstream-regulated gene (NDRG4), has been shown to bind the CDT of POPDC1. NDRG4 is a candidate tumor suppressor that is known to modulate cell migration, invasion, proliferation and angiogenesis [30][31][32]. The POPDC1–NDRG4 interaction was further shown to be essential in regulating the directional migration of epicardial cells [30]. In addition, disruptions to the POPDC1-NDRG4 interaction resulted in loss of directional migration and increased cell migration [30]. This suggests that the POPDC1–NDRG4 interaction is essential in controlling the direction and rate of migration in these cells.

In a similar fashion, the CTD domain of POPDC1 has been shown to interact with the guanine nucleotide exchange factor (GEFT) [29]. GEFT regulates the active state of GTPases such as Rac1 and RhoA which are known to regulate cell migration [33][34][35]. As previously discussed, the POPDC1–GEFT interaction is thought to potentially control migration via regulation of the activity of GTPases such as Rac1 and Cdc42. The POPDC–GEFT interaction could therefore represent another novel mechanism by which POPDC1 regulates cell migration.

Lastly, POPDC1 has also been implicated in the regulation of netrin-1-mediated cell migration and invasion. Netrin-1 belongs to the netrin family of extracellular proteins that guides the migration of cells and axons [36][37]. In cancer, netrin proteins regulate cell adhesion, migration, and survival [36]. In HCC, the expression of netrin-1 negatively correlates with *POPDC1* expression [18]. The overexpression of netrin-1 also suppressed POPDC1 expression in these cells suggesting that *POPDC1* is potentially regulated by netrin-1 in HCC. Given that both POPDC1 and netrin-1 are known to regulate migration and invasion, the effects of POPDC1 on netrin-1 mediated cell migration and invasion was tested. Interestingly, the upregulation of POPDC1 in HCC attenuated the ability of netrin-1 to enhance cell migration and invasion. This suggests that netrin-1 potentially enhances cell migration and invasion via a mechanism that entails POPDC1 suppression.

Taken together POPDC1 and POPDC3 regulate cell migration, invasion and metastasis. While various mechanisms by which POPDC1 potentially controls migration are known, further studies are warranted to clearly elucidate these mechanisms. Investigating the roles and mechanisms by which POPDC2 and POPDC3 potentially regulate migration, invasion and metastasis will also provide the much-needed clarity on how diverse the functions of POPDC proteins might be in various cancer types. Clarifying these mechanisms is thus essential to inform strategies on how these proteins can best be targeted in the treatment of pathologies such as cancer.

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