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The Popeye domain containing protein family – A novel class of cAMP effectors with important functions in multiple tissues

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ABSTRACT

Popeye domain containing (Popdc) proteins are a unique family, which combine several different properties and functions in a surprisingly complex fashion. They are expressed in multiple tissues and cell types, present in several subcellular compartments, interact with different classes of proteins, and are associated with a variety of physiological and pathophysiological processes. Moreover, Popdc proteins bind the second messenger cAMP with high affinity and it is thought that they act as a novel class of cAMP effector proteins. Here, we will review the most important findings about the Popdc family, which accumulated since its discovery about 15 years ago. We will be focussing on Popdc protein interaction and function in striated muscle tissue. However, as a full picture only emerges if all aspects are taken into account, we will also describe what is currently known about the role of Popdc proteins in epithelial cells and in various types of cancer, and discuss these findings with regard to their relevance for cardiac and skeletal muscle.

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1. The Popeye domain containing gene family

The first member of the Popdc gene family was independently discovered by two groups through subtractive hybridisation aiming at the identification of novel transcripts with a cardiac muscle-restricted expression pattern (Andrée et al., 2000; Reese et al., 1999). Reese and colleagues named the novel gene *Blood vessel epicardial substance (Bves)*, which was based on the expression pattern they observed by immunolabelling (Reese et al., 1999). Due to the high expression level in striated muscle tissue, Andrée et al. gave it the name *Popeye1 (Pop1)*, which is a reference to the comic-strip hero "Popeye the sailor", who is most famous for his super-natural muscle strength (Andrée et al., 2000). They also discovered two other related genes expressed in higher vertebrates, and referred to them as *Pop2* and *Pop3*, in order to indicate their membership to the same gene family. Today, these genes are known as the Popeye domain containing (Popdc) genes *Popdc1, Popdc2, and Popdc3* (Brand et al., 2014). In addition, the name *Bves* is still used as a synonym for *Popdc1*.

2. Evolutionary background

Popdc genes are found throughout the animal kingdom and are already present in *Hydra* and other *Cnidaria* indicating that their roots lie at the base of metazoan evolution (reviewed in Brand et al., 2014). Significantly, at the sequence level Popdc proteins are highly conserved suggesting that they have an important and essential role. In vertebrates three Popdc genes are present, while in lower chordates two genes are found (Brand, 2005). In man, *Popdc1* and *Popdc3* are found on human chromosome 6q21 as tandem arrayed genes, while *Popdc2* is localised on human chromosome 3q13.33 (Andrée et al., 2000). The tandem array organisation of *Popdc1* and *Popdc3* genes is already present in lower chordates, suggesting that this genomic organisation may have some role at the gene regulatory level. However, it is noteworthy in this context that in addition to gene-specific transcripts a number of vertebrate species are predicted to generate also transcripts, which do not obey the gene boundaries. These transcripts would encode a Popdc3/Popdc1 fusion protein (Andrée et al., 2000), however, presently the functional significance thereof is unknown. *Drosophila* is unique in a having a single Popdc gene, while most invertebrates have two genes. Some species show a higher level of gene duplication (Brand et al., 2014). Interestingly, Popdc proteins show some sequence homology to the bacterial transcription factors Catabolite Activator Protein (CAP) and cAMP Receptor Protein (CRP), which are involved

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in metabolic regulation. It is therefore possible that these prokaryotic transcription factors and the transmembrane Popdc proteins, which are found in metazoans have a common evolutionary origin (Schindler et al., 2012; Simrick et al., 2013).

3. Expression pattern of Popdc proteins

All three members of the Popdc gene family are expressed in cardiac and skeletal muscle (Andrée et al., 2000; Breher et al., 2004). In the heart, *Popdc1* expression in the embryonic heart is equally strong in both atrial and ventricular chambers, whereas postnatally, *Popdc1* expression is weaker in ventricular compared to atrial myocardium. *Popdc2* on the other hand is expressed at equal levels in both chamber types. The highest expression level for *Popdc1* and *Popdc2* is observed in the cardiac conduction system including the sinoatrial (SAN) and atrioventricular nodes (AVN) (Froese et al., 2012).

There still exists some controversy with regard to the cell types in the heart that express *Popdc1*. The first report of the cardiac Popdc1 expression pattern at the protein level by David Bader and colleagues described an expression in the epicardium and the coronary vasculature (Reese et al., 1999). However, β-galactosidase (LacZ) staining of tissues from a *Popdc1-LacZ* knockin mouse, revealed expression in cardiac myocytes and absence of staining in the epicardium, coronary arteries and other nonmuscle cell types (Andrée et al., 2002a). Moreover, immunohistochemistry, *in situ* hybridisation, and RT-PCR analysis of the chick and mouse heart did not reveal any expression in the proepicardium, epicardium or coronary vasculature (Andree et al., 2002a, 2002b; Torlopp et al., 2006).

It is noteworthy that in addition to the abundant expression in striated muscle tissue, Popdc1 is also present in smooth muscle cells of bladder, uterus, and the gastrointestinal tract, as well as in the brain, various epithelia, spinal ganglia, thymus, testes, stomach, lungs, kidneys, and spleen (Andree et al., 2000; Hager and Bader, 2009; Osler and Bader, 2004; Osler et al., 2006; Reese et al., 1999; Ripley et al., 2004; Smith and Bader, 2006; Torlopp et al., 2006; Vasavada et al., 2004). The expression pattern of *Popdc2* has also been analysed and display strong overlap with *Popdc1*, however some differences have also been observed (Froese and Brand, 2008; Froese et al., 2012). Due to a lack of immunoreagents and appropriate mouse models, *Popdc3* expression has not yet been extensively studied. However, preliminary data revealed an expression pattern similar to *Popdc1* (Andree et al., 2000). Immunofluorescent analysis of the subcellular localisation of Popdc1 and Popdc2 proteins in cardiac myocytes established a strong labelling of the plasma membrane, with all three membrane compartments being labelled, i.e. the intercalated disk, the lateral membrane and the t-tubules (Froese et al., 2012).

4. Structure and biochemical properties of Popdc proteins

Popdc proteins are three-pass transmembrane proteins with a short extracellular amino-terminus, which contains up to two N-glycosylation sites (Andrée et al., 2000; Knight et al., 2003). Glycosylation is quite extensive in these proteins and significantly affecting the electrophoretic mobility in SDS-PAGE. Popdc1 for example runs at 58 kDa, while the protein sequence predicts a molecular weight of about 42 kDa. Interestingly, the extent of glycosylation and therefore electrophoretic mobility is tissue-dependent (Vasavada et al., 2004). Thus, POPDC1 protein isolated from chicken heart and skeletal muscle runs at 58 and 70 kDa, respectively. Possibly the size differences are based on tissue-specific regulation of glycosylation. The impact of glycosylation on Popdc function is presently unknown, however, it has been hypothesised that it may play a role in membrane localisation of Popdc proteins or protect them from proteolytic decay (Hager and Bader, 2009). Importantly, Popdc proteins form homodimers, which are stabilised by disulfide bonds and may be necessary for the maintenance of epithelial integrity and junctional stability (Hager and Bader, 2009). How homodimerisation is mediated is presently unclear. Although it has been previously reported that conserved lysines at the carboxy-terminal end of the Popeye domain of Popdc1 mediate homodimerisation (Kawaguchi et al., 2008), it was subsequently shown that Popdc1 protein lacking this sequence motif is still able to homodimerise, suggesting that there are probably also other protein domains involved, which have not yet been identified (Russ et al., 2011). The C-terminus of Popdc proteins is located in the cytoplasm and contains the Popeye domain (PFAM: PF04831), which consists of about 150 amino acids and shows high sequence conservation (Andree et al., 2000). The Popeye domain harbours a functional cyclic nucleotide binding domain (CNBD), which enables Popdc proteins to specifically bind to and be modulated by adenosine 3′,5′-cyclic monophosphate (cAMP). Popdc proteins probably do not bind guanosine 3′,5′-cyclic monophosphate (cGMP), since the affinities for both cyclic nucleotides differ by a factor of about 40 (Froese et al., 2012). Thus, Popdc proteins are one of only five classes of eukaryotic cAMP effector proteins, which, apart from protein kinase A (PKA), include exchange protein directly activated by cAMP (Epac), and hyperpolarisation-activated cyclic nucleotide-gated cation (HCN) channels (Rehmann et al., 2007). Recently, a sperm-specific novel cyclic nucleotide receptor (CRIS) has been reported (Krahling et al., 2013). Although the Popeye domain is predicted to be structurally similar to other cAMP binding domains, at the sequence level only very limited similarity is present. The actual phosphate binding cassette (PBC), which makes contact to the cyclic nucleotide is very different and does not resemble the PBC found in the other cAMP effector proteins (Brand et al., 2014). Using a radioligand binding assay and by FRET analysis, Froese and colleagues have demonstrated that the cAMP affinity of Popdc proteins is about 10-fold higher than that of Epac1 and similar to that of PKA (Froese et al., 2012). Charge-to-alanine mutations of an invariant aspartate residue (D200 in Popdc1 and D184 in Popdc2), which is part of the ultra-conserved DSPE sequence motif present in most POPDC proteins and thought to be part of the CNBD, eradicated cAMP binding, suggesting that this residue is crucial for cyclic nucleotide binding (Froese et al., 2012). Carboxy-terminal to the Popeye domain is a sequence, which is variable in length amongst Popdc family members. In Popdc1 this carboxy-terminal sequence is rich in acidic amino acids and contains an array of serine/threonine residues, which are subject to phosphorylation after β-adrenergic stimulation (Lundby et al., 2013).

5. Functional impact of the Popeye domain containing protein family

5.1. Popdc1 is involved in cell–cell contact formation and regulates epithelial function

Popdc1 has been shown to be an essential component of tight junctions and to be important for proper epithelial function. In mature epithelia including murine small intestine epithelium, Popdc1 was found to co-localise with constituents of the tight junction complex such as occludin, and a direct interaction of Popdc1 and ZO-1 has been established by GST pull-down (Osler et al., 2005). It has been hypothesised that via this protein–protein interaction Popdc1 plays an important role in the formation and maintenance of epithelial monolayers. In human corneal epithelial cells, Popdc1, presumably through interaction with ZO-1,

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