Cellular Signalling 25 (2013) 93–100

Contents lists available at SciVerse ScienceDirect

Cellular Signalling

journal homepage: www.elsevier.com/locate/cellsig

Review

Beyond cell adhesion: The role of armadillo proteins in the heart

David Swope, Jifen Li, Glenn L. Radice *

Center for Translational Medicine, Department of Medicine, Jefferson Medical College, Philadelphia, PA, USA

ARTICLE INFO

Article history:
Received 10 September 2012
Accepted 24 September 2012
Available online 27 September 2012

Keywords:
Plakoglobin
β-catenin
Cadherin
Adherens junction
Desmosome
Wnt signaling
Arrhythmogenic right ventricular cardiomyopathy (ARVC)

ABSTRACT

Plakoglobin (PG, γ-Catenin, JUP), a member of the armadillo protein family and close homolog of β-catenin, functions to link cell surface cadherin molecules with the cytoskeleton. PG is the only junctional component found in both desmosomes and adherens junctions and thus plays a critical role in the regulation of cell–cell adhesion. Similar to β-catenin, PG is able to interact with components of the Wnt signaling pathway and directly affect gene expression by binding with LEF/TCF transcription factors. In addition, it has been proposed that PG functions primarily as a competitive inhibitor of β-catenin transcriptional activity by sequestering LEF/TCF. Compared to β-catenin, the contribution of PG as a transcriptional regulator in either physiological or pathological conditions is poorly understood. There is increasing clinical interest in PG as both a structural protein as well as a signaling molecule as mutations have been identified in the human PG gene that cause Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) and cutaneous syndromes. This review will discuss the connection between altered cell adhesion and gene expression and its contribution to disease pathogenesis.

Contents

1. Introduction

Plakoglobin (PG, γ-catenin, JUP) was initially described as a component of multiple intercellular mechanical junctions [1]. It was later found to be homologous to the *Drosophila* segment polarity gene; *armadillo* (arm) [2,3]. Shortly following the discovery of PG, another arm family member was recognized as β-catenin (CTNNB1). Initially, it was proposed that PG and β-catenin might be the same molecule as they were so closely related, however further studies soon revealed two distinct proteins [4,5]. Over the years β-catenin has been extensively studied (~14,000 articles PubMed), compared with the enigmatic PG molecule (~1300 articles). This discrepancy is due to the well-established signaling capacity of β-catenin as part of the Wnt pathway and as such its importance in developmental biology, tissue

* Corresponding author at: Center for Translational Medicine, Department of Medicine, Jefferson Medical College, Rm 309 College Bldg., 1025 Walnut St., Philadelphia, PA 19107, USA. Tel.: +1 215 503 5157; fax: +1 215 503 5731.
E-mail address: glenn.radice@jefferson.edu (G.L. Radice).

0898-6568/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.cellsig.2012.09.025

regeneration and disease pathogenesis. In contrast, current opinions regarding the physiological significance of PG as a transcriptional regulator remain controversial.

Armadillo protein family members have a central "armadillo" domain containing 13 imperfect repeats of 42 amino acids which is flanked by distinct amino (N-) and carboxy (C-) terminal domains [6]. The positively charged groove of the arm domain is organized as α-helixes and mediates numerous protein-protein interactions discussed below. The central arm domain of PG and β-catenin has 83% amino acid similarity while the N- and C-terminal tails share 57% and 15% similarity, respectively (Fig. 1) [7]. The relatively low homology between the terminal tails likely contributes to disparate binding partners and functional activity of these otherwise closely related armadillo family members. This review will focus on PG and β-catenin as structural proteins and their roles in signal transduction in the heart. We will discuss recent evidence supporting an unexpected role for PG as a negative regulator of Wnt/β-catenin signaling in cardiac progenitor cells and its relevance to the unique fibro-fatty pathology observed in ARVC patients.

2. Functional overlap and distinct roles for PG and β-catenin

2.1. Armadillo protein function in cell adhesion

Desmosomes and adherens junctions act as mechanical cell–cell adhesion junctions maintaining the structural integrity of the tissue. Adherens junctions are comprised of classical single membrane pass cadherins that bind to like cadherins on neighboring cells, forming a cell adhesive zipper [8]. PG and β-catenin bind to the cytoplasmic tail of cadherins in a mutually exclusive manner. E-cadherin binds PG directly between arm repeats 4–5 [4,9], while N-cadherin binds to repeats 7–8 [10]. PG and β-catenin mediate linkage of cadherins to the actin cytoskeleton via α-catenin, although not necessarily through a direct physical link [11]. Arm repeat 1 has been shown to be essential for PG interaction with α-catenin [10,12–14] (Fig. 1). Desmosomes also provide cell–cell adhesion, but do so through intracellular connection to the intermediate filament system. PG plays a critical role in linking the desmosomal cadherins, desmoglein (DSG) and desmocollin (DSC), to the cytoskeleton via desmoplakin (DP). Plakophilin, another member of the armadillo protein family, like PG binds to the cytoplasmic domain of DSG and DSC and serves to link the transmembrane proteins to the cytoskeleton [15,16]. Similar to adherens junctional components, desmosomal cadherins bind the central arm repeats of PG [17–26] (Fig. 1). PG and β-catenin bind with similar affinities to E-cadherin, whereas PG binds to DSG-1 stronger than does β-catenin [27]. Moreover, β-catenin fails to recruit DP and anchor desmosomal cadherins to intermediate filaments in PG-null cells [28,29]. Therefore, β-catenin cannot functionally replace PG in desmosomal junctions. This is an important distinction as PG mutations are associated with a cardiocutaneous syndrome that is likely explained by altered cell adhesion in the heart and skin of those patients. This topic will be discussed later in relation to the genetic disease arrhythmogenic right ventricular cardiomyopathy (ARVC).

Proper mechanical and electrical coupling of cardiomyocytes is crucial for normal propagation of the electrical impulse throughout the working myocardium. Junctional proteins concentrated at the termini of cardiomyocytes are responsible for the integration of structural information and cell-cell communication. The end-to-end connection between cardiomyocytes called the intercalated disc (ICD) consists of three main junctional complexes: adherens junctions, desmosomes, and gap junctions. The gap junction provides intercellular communication via small molecules and ions that pass through a channel generated by a family of proteins called connexins. Gap junctions allow for electrical coupling of cardiomyocytes ensuring coordinated muscle contraction required for proper heart function. There is a growing appreciation for the integrated nature of the junctional complexes at the ICD and how aberrant cell–cell coupling mediated through these junctions can lead to cardiomyopathy and an increased risk of arrhythmias.

2.2. Armadillo protein function in signal transduction

The Wnt signal transduction pathway controls a variety of biological phenomena throughout development and adult life of all animals [30]. Aberrant Wnt signaling underlies a wide range of pathologies in humans. β-catenin is a well-established downstream effector of the Wnt signaling cascade. In contrast, whether PG is a positive or negative regulator of Wnt signaling remains a matter of discussion. PG and β-catenin co-exist in a tightly regulated cytoplasmic pool between membrane associated forms and nuclear localization (Fig. 2). Cytosolic pools of β-catenin/PG are managed by canonical Wnt signaling and ubiquitin–proteasome-dependent degradation. The targeting of β-catenin/PG degradation is achieved through the phosphorylation of N-terminal serine residues by a multi-protein "destruction complex" containing glycogen synthase kinase 3β (GSK3β) and scaffold proteins adenomatous polyposis coli (APC) and axin [31–33]. The GSK3β-dependent phosphoserine motif of PG is recognized by the ubiquitin ligase β-TrCP that targets PG for degradation via the 26S proteasome [34]. Degradation of β-catenin/PG by the destruction complex is regulated by the binding of Wnt to its receptor, frizzled (FRZ) and transactivation of scaffold protein, disheveled (DSH) [35]. Activated DSH recruits GSK-binding protein (GBP/FRAT) and protein phosphatase 2C leading to the disassembly of the destruction complex and accumulation of β-catenin/PG in the nucleus [36–42]. Despite the fact that these proteins interact with the same degradation machinery, PG protein stability does not appear to be as tightly controlled as β-catenin. Mutations in the GSK3β phosphorylation domain of β-catenin (e.g. S37A) cause a dramatic increase in cytoplasmic levels of the protein and its signaling activity. However, the analogous N-terminal mutation in PG

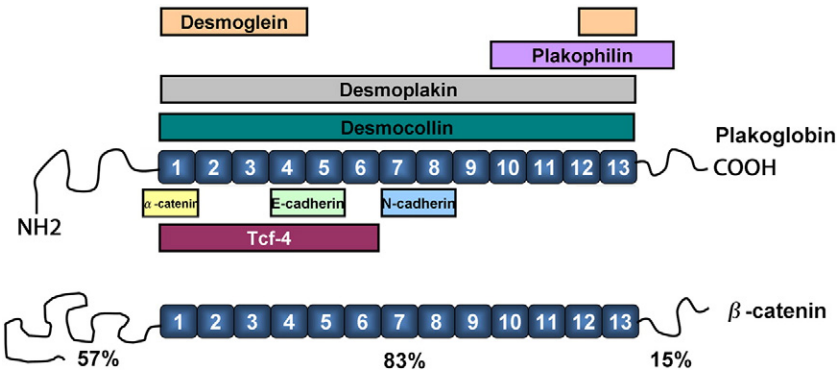

Fig. 1. Plakoglobin and β-catenin have similar structure. Schematic representation of plakoglobin and β-catenin protein including the 13 *armadillo* repeats. PG and β-catenin share many of the same binding partners as shown above (boxes). Percent amino acid similarity between the central 'armadillo' domain and N- and C-terminus are shown below.