Seminars in Cell & Developmental Biology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

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

Review

Regulation of cellular and PCP signalling by the Scribble polarity module

Michal Milgrom-Hoffman[a], Patrick O. Humbert[a,b,c,*]

[a] Department of Biochemistry & Genetics, La Trobe Institute for Molecular Science, La Trobe University, Melbourne, Victoria 3086, Australia
[b] Department of Biochemistry & Molecular Biology, University of Melbourne, Melbourne, Victoria 3010, Australia
[c] Department of Pathology, University of Melbourne, Melbourne, Victoria 3010, Australia

ARTICLE INFO

Article history:
Received 22 October 2017
Received in revised form
11 November 2017
Accepted 13 November 2017
Available online xxx

Keywords:
Scribble
Dlg
Lgl
Cell polarity
Planar cell polarity
PCP
Signaling
Cancer

ABSTRACT

Since the first identification of the Scribble polarity module proteins as a new class of tumour suppressors that regulate both cell polarity and proliferation, an increasing amount of evidence has uncovered a broader role for Scribble, Dlg and Lgl in the control of fundamental cellular functions and their signalling pathways. Here, we review these findings as well as discuss more specifically the role of the Scribble module in PCP signalling.

Contents

* Corresponding author at: Department of Biochemistry & Genetics, La Trobe University, Melbourne, Victoria 3086, Australia.
E-mail address: p.humbert@latrobe.edu.au (P.O. Humbert).

https://doi.org/10.1016/j.semcdb.2017.11.021
1084-9521/

1. Introduction

Directionality, or polarity, is a fundamental cellular property that together with proper coordination of proliferation, survival and differentiation control is essential for the organisation, development and normal function of all living tissues. Cell polarity is established through the asymmetric distribution of proteins, lipids and RNA, creating specialized cell functions (reviewed in Refs. [1,2]). Several major types of cell polarity states have been described, characterised by their biological context, and the signalling pathway and cell polarity complexes that take part in establishing polarity and cellular function. Apical-Basal Cell Polarity (ABCP) is most commonly associated with the term cell polarity and the best understood. In an epithelial context, it helps generate and maintain the architecture of the cell within the epithelial tissue including defining an apical membrane facing a lumen, lateral adhesions between neighbouring cells, and basal attachment to the extracellular cellular matrix (ECM). Asymmetric cell division (ACD) is a form of cell polarity utilised to regulate the self-renewal of stem cells and differentiation of the progenitor cells, with Front-Rear cell polarity (FRCP) referring to the regulation of directional migration. Although a common phenomenon, and implicated in an array of developmental processes as well as tumorigenesis, much less is known about the molecular mechanisms governing Planar Cell Polarity (PCP) initiation and maintenance. The Scribble module and each of its components Scrib, Dlg and Lgl, have been shown to be highly conserved and to participate in maintaining a variety of cellular polarity states. Here we focus on the role of the Scribble polarity module in cellular and PCP signalling, linking signalling pathways to asymmetric distribution of structural components and ultimately, tissue polarity.

2. The Scribble polarity module

The Scribble module was first identified in *Drosophila melanogaster* (reviewed in Refs. [3,4] and named after the various phenotypes of their respective mutants including disorganized epithelium and abnormal cuticle deposition (*scribbled*, *scrib*), overgrowth of larval tissues (*discs large*, *dlg*) or overgrowth of the whole larva itself leading to its untimely death (*lethal giant larvae*, *lgl*). Scrib was found to function as a genetic and functional module together with Dlg, a membrane-associated guanylate kinase (MAGUK) protein and Lgl (WD40 repeat-containing protein), with all three components initially shown to have identical effects on epithelial cells [5]. Consistent with their proposed roles as site-specific signalling adaptors, the Scribble module proteins are characterised at a structural level by the presence of multiple protein–protein interaction domains, including PSD-95/Dlg/ZO-1 (PDZ), Leucine-Rich Repeat (LRR), Src Homology 3(SH3), WD40-repeat (WD40) and Guanylate Kinase-like (GuK) domains (Fig. 1). Specifically, Scribble is a LAP family protein (LRR and PDZ) containing a 16 LRRs N-terminal region that is predicted to form a β-sheet [6], and four PDZ homology domains [7,8]. The Scribble LRR and PDZ domains are required for proper localization of Scribble to the basolateral membrane of epithelial cells [9–11], with recent studies implicating a key role for a S-palmitoylation regulated by ZDHHC7 and APT2 to control Scribble localisation and hence function [12,13]. Indeed, specific mutations in various domains of Scribble can lead to its mislocalisation and loss of function-like phenotypes in *C. elegans* [11], *Drosophila* [10], mice [6], and likely in human germline mutant patients [14–16] (See Fig. 1). Furthermore, phosphorylation or altered interactions of Scribble, Dlg, or Lgl with their other binding partners may also cause mislocalization (reviewed in Ref. [17]). Thus, a combination of protein–protein interactions and post-translational modifications cooperate to regulate proper localisation of Scribble and Dlg *in vivo*. Similarly, aPKC-dependent phosphorylation of Lgl regulates its dissociation from the cell cortex, which in turns alters its ability to interact with many proteins and thus affects its function in apicobasal polarity and cell proliferation control [17–19]. Despite the large body of work defining the Scribble module genetically and functionally, how the Scribble module proteins actually interact with each other at a physical level though is still poorly understood. The interaction of Dlg with Lgl requires Serine phosphorylation of Lgl in its linker region [20]. Furthermore, both in *Drosophila* and zebrafish, the protein GUK-holder (NHS in vertebrates) serves to scaffold Scribble and Dlg [21,22]. A better understanding of the physical interactions between Scribble module proteins and how they are regulated at a biochemical and structural level is still required.

Like other cell polarity determinants, Scribble polarity proteins are highly conserved in sequence among different species [23]. Consistent with this, there is a large body of evidence for the functional conservation of Scribble, Dlg and Lgl with the vertebrate homologues able to rescue polarity defects and tumorous overgrowth of the respective *Drosophila* mutants [24–26]. In mammals four corresponding Dlg homologues exist, Dlg1/SAP97, Dlg2/PSD93, Dlg3/SAP102 and Dlg4/PSD95, which all display the characteristic MAGUK structural domains of their *Drosophila* homologue. In addition, two Lgl (Llgl1, Llgl2) and only one single Scribble homologue exist in higher vertebrates. The human Scribble (hScrib/SCRIB) gene shows high homology to the *Drosophila* Scrib and colocalizes with Dlg family members [4].

Of note, other members of the LAP protein family such as Densin-180, Erbin and Lano have been described to have similar basolateral localization and overlapping biological functions with Scribble (reviewed in Ref. [7]). Densin-180 is a neuron-specific protein and the first mammalian LAP protein to be described [27]. Erbin is associated with the ERBB2/HER2 tyrosine kinase receptor in epithelial cells [28] and implicated in mammary tumour progression [29]. Lano appears only present in vertebrates and can directly interact with Dlg1 and Erbin [30]. Although these LAP proteins share the conserved Scribble LRR domain, they only contain one (Densin and Erbin) or no PDZ domains (LANO) [7] which may account for some of the reported differential requirement for these proteins in cell polarity regulation.

A wealth of information ties the Scribble module to regulation of the actin cytoskeleton, cell signalling, vesicular trafficking and cell proliferation control, as well as to the variable forms of cell polarity (reviewed in Refs. [19,17]). The Scribble module's contribution to apicobasal polarity and ultimately, barrier function in epithelial cells, is maintained through antagonistic interactions with the other well characterised cell polarity complexes namely the Par (Par3, Par6, aPKC) and Crumbs (Crb, Pals1, PatJ) complexes located at the apical membrane. The Crumbs Complex and the Par complex through aPKC-mediated phosphorylation exclude Lgl from the apical cortex to maintain Scrib basolateral localization [19,17]. In addition to its roles in apicobasal polarity, the Scribble module also regulates a number of other polarity states. Studies in *Drosophila* neural progenitor cells [31,32], vertebrate neural tube formation [33], and T lymphocytes [34–36] have all established a role for the Scribble module in various forms of asymmetric cell division (ACD). All Scribble module proteins also regulate front-rear cell polarity and directed cell migration through a number of mechanisms ultimately regulating the assembly of microtubules and the actin cytoskeleton (reviewed in [37,18]). Furthermore, the mammalian Dlg homologues were first characterised as post-synaptic density scaffolding proteins, and together with other Scribble module proteins are expressed in neurons and required for normal synaptic structure and function in both invertebrates and vertebrates (reviewed in [22,38–42]). Finally, the Scribble module serves an important role in planar cell polarity (PCP) (see below) a process

Please cite this article in press as: M. Milgrom-Hoffman, P.O. Humbert, Regulation of cellular and PCP signalling by the Scribble polarity module, Semin Cell Dev Biol (2017), https://doi.org/10.1016/j.semcdb.2017.11.021