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Review Article

Dissecting the role of polarity regulators in cancer through the use of mouse models

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ABSTRACT

Loss of cell polarity and tissue architecture is a hallmark of aggressive epithelial cancers. In addition to serving as an initial barrier to tumorigenesis, evidence in the literature has pointed towards a highly conserved role for many polarity regulators during tumor formation and progression. Here, we review recent developments in the field that have been driven by genetically engineered mouse models that establish the tumor suppressive and context dependent oncogenic function of cell polarity regulators *in vivo*. These studies emphasize the complexity of the polarity network during cancer formation and progression, and reveal the need to interpret polarity protein function in a cell-type and tissue specific manner. They also highlight how aberrant polarity signaling could provide a novel route for therapeutic intervention to improve our management of malignancies in the clinic.

Contents

Abbreviations: AB, Apical-Basal; ACD, Asymmetric Cell Division; AJ, Adherens Junctions; AMPK, AMP-Activated Protein Kinase; CSC, Cancer Stem-Cell; EMT, Epithelial-to-Mesenchymal Transitions; FR, Front-Rear; Fzd, Frizzled; PCP, Planar Cell Polarity; TJ, Tight Junctions; ZO-1/2, Zonula Occludens-1/2.

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Introduction

Several modes of cell polarity are critical for embryonic development and tissue homeostasis. Much research has been devoted to delineating how functional epithelial tissue organization is established and maintained by apical-basal (AB) cell polarity, within an individual epithelial cell, and planar cell polarity (PCP) that polarizes the plane of a tissue across the proximal-distal axis [1–4]. Evolutionary conserved AB polarity and PCP proteins mediate the correct assembly and positioning of cell:cell junction complexes (e.g. adherens and tight junctions (AJ/TJ) and cytoskeletal rearrangements necessary to create functional and spatially distinct domains within a polarized cell [1,5]. In addition, front-rear (FR) polarity coordinates cellular events required for migration, while stem cell division polarity is fundamental for asymmetric cell divisions (ACD) that enables self-renewal and differentiation.

Several genetic and biochemical approaches, primarily utilizing invertebrate model organisms and mammalian cell lines *in vitro*, have established a clear role for loss of polarity in cancer [1–5]. However, numerous core polarity regulators are now emerging as tumor suppressors during multiple stages of disease progression in vertebrate animal models, including tumor initiation, which contrasts with the prior view that loss of polarity is simply a consequence of tumor progression. These *in vivo* platforms provide valuable tools to dissect out the molecular basis for how aberrant polarity signaling causes tumorigenesis and facilitates malignant progression. This review focuses on the tumor suppressive and/or oncogenic function of core polarity modules during tumor initiation, growth and progression, centering on recent mouse models of cancer. These include members of the Par, Scrib and Crumbs polarity modules that play a central role in establishing and maintaining AB and more general epithelial polarity, as well as Lkb1, Gpsm2 and PCP pathway components involved in more specific aspects of tissue architecture and homeostasis. The tumor suppressive roles of the junctional proteins that help establish and maintain cell polarity are reviewed in detail elsewhere [6–8]. In addition, we have limited our discussion to epithelial derived cancers, however many of the broader points are likely to apply to tumors of other origin, such as leukemias [9].

The core polarity modules and cancer

The Par complex

In mammals, the Par complex comprises partitioning defective protein 3 and 6 isoforms (Par3α/β, Par6α/β/γ), atypical protein kinase C (aPKCι/ζ) and the small GTPase cell division control protein 42 (Cdc42) (reviewed in [1,2]). The Par complex is apically restricted *via* phospholipids, cell adhesion molecules and by basolateral polarity proteins that act in a reciprocal antagonistic relationship with apical polarity regulators to maintain AB cell polarity [1,2]. The Par complex functions to stabilize cell:cell junctions [10,11], and can mediate FR polarity in migrating cells through the forward localization of Par3, aPKC and Cdc42 [5]. Furthermore, both Par3 and Par6 are required for collective cell migration [12] and loss of Par3, Par6, aPKC or Cdc42 can result in spindle orientation defects [1,2]. Notably in *Drosophila*, the G-protein signaling modulator-2 (Gpsm2) asymmetric cell division (ACD) complex is tethered to par3 *via* Inscuteable (insc), and in mammalian cells, aPKC controls spindle orientation by phosphorylating GPSM2 [1,2]. Together, this evidence provides a cellular rationale for the tumor suppressor/oncogenic activities associated with aberrant expression of Par complex members.

Consistent with this notion, Par complex members are frequently deregulated in cancer (reviewed in detail in [1,2]). For instance, Par3 expression is significantly reduced or lost in glioblastoma, esophageal squamous carcinoma, and breast, lung, head and neck cancer patients [1,2]. Nevertheless, overexpression of Par3 correlates with poor outcome in renal cancer patients, highlighting the context dependent roles of polarity proteins. Consistent with its role as a proto-oncogene, Par6 is overexpressed/amplified in breast and lung cancers and aPKCι/λ is overexpressed/amplified in many cancers including hepatocellular carcinoma, esophageal squamous carcinoma, and breast, ovarian, pancreatic, and lung cancers [1,2,13,14]. Conversely, aPKCζ is down-regulated or mislocalised in colorectal, ovarian and bladder cancer [1], suggesting that in some cases aPKC isoforms can be functionally divergent during cancer progression.

Mouse models have been essential to improve our understanding of the functional significance of genetic alterations in polarity genes for cancer formation and progression *in vivo*. Mammary transplant models have now demonstrated that Par3 deficiency is sufficient to cause ductal hyperplasia in mice, but does not predispose to malignant disease [15]. These data suggest that an additional oncogenic event is required for Par3 loss to contribute to cancer progression. Indeed, two independent studies have recently demonstrated that loss of Par3 can cooperate with an additional oncogenic event *in vivo* (*e.g.* ErbB2/Ras/Notch activation) to accelerate mammary tumor growth and increase metastatic potential [11,16]. Further investigation established that Par3 depletion could facilitate progression *via* extracellular matrix remodeling, reduced cell:cell junction stability/cohesion and aberrant activation of Rac-Tiam1 signaling [11,16]. In addition, Par3 has recently been shown to regulate the ACD protein Gpsm2 to promote oriented cell divisions during murine epidermal morphogenesis [17]. Nevertheless, despite the critical role revealed for Par3 during mammary gland morphogenesis and progenitor function [15], Huo et al. recently reported that Par3-Like (Par3L) suppression of Lkb1 (Serine-threonine kinase 11, STK11) kinase activity, and not Par3, is essential for murine mammary stem cell function [18]. Together, these findings highlight the need for future work addressing the