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Review

Cellular and molecular mechanisms underlying planar cell polarity pathway contributions to cancer malignancy

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ABSTRACT

While the mutational activation of oncogenes drives tumor initiation and growth by promoting cellular transformation and proliferation, increasing evidence suggests that the subsequent re-engagement of largely dormant developmental pathways contributes to cellular phenotypes associated with the malignancy of solid tumors. Genetic studies from a variety of model organisms have defined many of the components that maintain epithelial planar cell polarity (PCP), or cellular polarity in the axis orthogonal to the apical-basal axis. These same components comprise an arm of non-canonical Wnt signaling that mediates cell motility events such as convergent extension movements essential to proper development. In this review, we summarize the increasing evidence that the Wnt/PCP signaling pathway plays active roles in promoting the proliferative and migratory properties of tumor cells, emphasizing the importance of subcellular localization of PCP components and protein–protein interactions in regulating cellular properties associated with malignancy. Specifically, we discuss the increased expression of Wnt/PCP pathway components in cancer and the functional consequences of aberrant pathway activation, focusing on Wnt ligands, Frizzled (Fzd) receptors, the tetraspanin-like proteins Vangl1 and Vangl2, and the Prickle1 (Pk1) scaffold protein. In addition, we discuss negative regulation of the Wnt/PCP pathway, with particular emphasis on the Nrdp1 E3 ubiquitin ligase. We hypothesize that engagement of the Wnt/PCP pathway after tumor initiation drives malignancy by promoting cellular proliferation and invasiveness, and that the ability of Wnt/PCP signaling to supplant oncogene addiction may contribute to tumor resistance to oncogenic pathway-directed therapeutic agents.

Contents

1. Introduction

Tremendous effort over the last four decades has been spent unraveling the molecular mechanisms that contribute to cancer ini-

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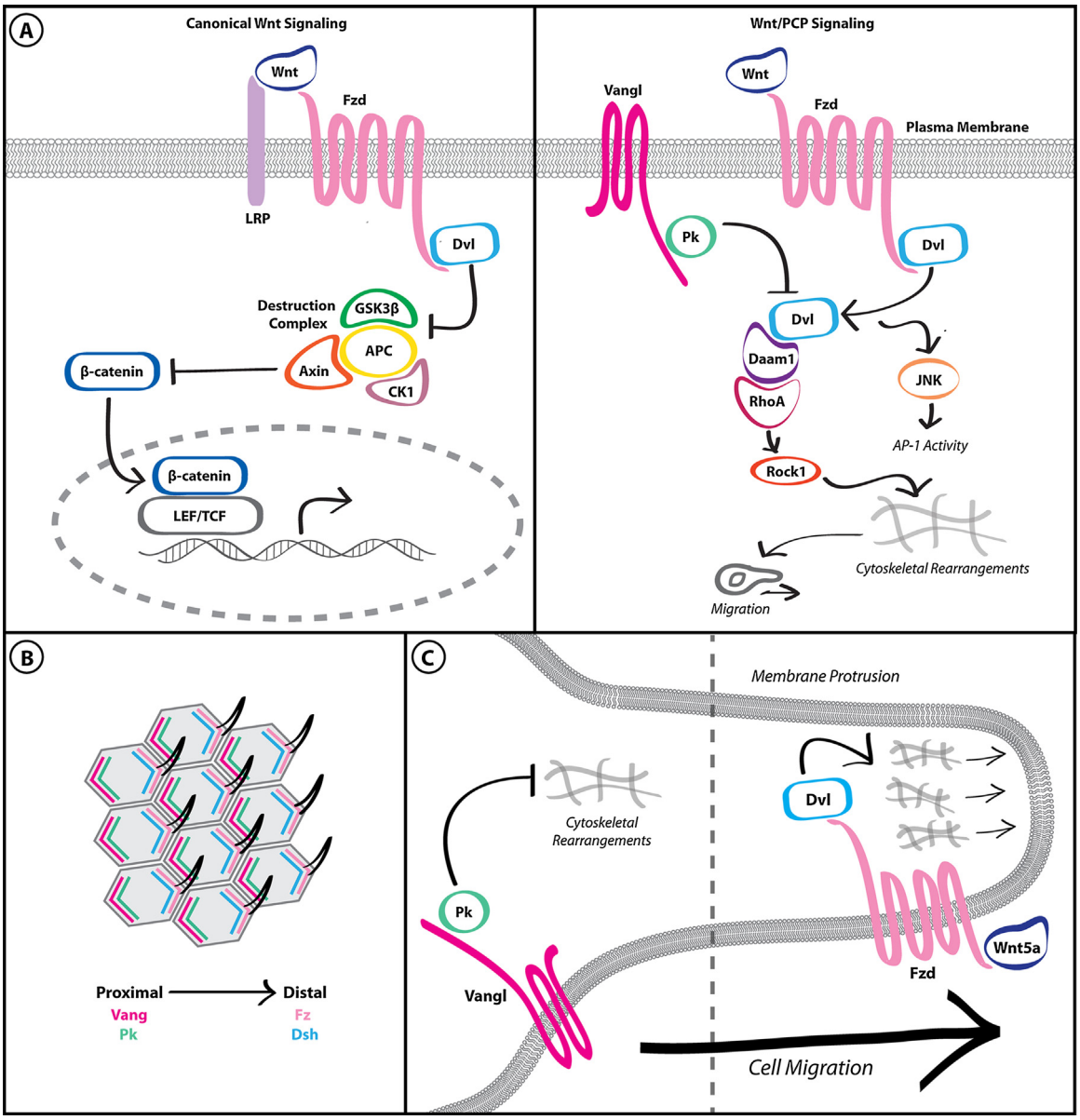

Fig. 1. Wnt/PCP signaling is distinct from canonical Wnt signaling and is adapted to promote cancer cell migration. A. Canonical Wnt signaling results in inhibition of the "destruction complex" and β-catenin-dependent transcription (left panel). In contrast, Wnt/PCP signaling results in mutual antagonism between Fzd/Dvl and Vangl/Pk complexes, leading to cytoskeletal rearrangements (right panel). B. The asymmetric distribution of core PCP complexes in the developing *Drosophila* wing results in consistent distal localization of the wing hair throughout the tissue. C. Wnt/PCP pathway activation within individual breast cancer cells results in asymmetric localization of core PCP components in a manner analogous to PCP in polarized epithelial cells. These complexes promote or restrain actin cytoskeletal dynamics, resulting in directed migration.

tiation and tumor development, which has led to the identification of a plethora of oncogenes that drive cellular transformation and proliferation. However, most attempts to therapeutically inhibit oncogenic drivers and their associated growth signaling pathways have yielded only incremental improvements in patient outcomes. While secondary mutations in oncogenic driver pathways can subvert therapeutic efficacy, tumors also engage alternative pathways that promote malignancy and contribute to drug resistance.

Aggressive, invasive tumors arise not only from dysregulated proliferation and differentiation pathways, but also from the breakdown of cellular polarity programs. Cellular architecture within the simple epithelial sheets lining many tissues is organized along two axes: (1) the commonly studied apical-basal axis responsible for the separation of apical components associated with epithelial function from basal components involved in adhesion and signaling, and (2) the planar axis orthogonal to the apical-basal axis that organizes cell polarity across the surface of the epithelial sheet. Cell polarity is intimately connected to homeostatic cell function, and disruptions to apical-basal polarity genes can sensitize cells to oncogenic transformation [1,2]. Recent studies have revealed critical contributions of the under-appreciated planar cell polarity (PCP) pathway to tumor progression, which suggest that a deeper understanding of this pathway may yield valuable insights into tumor biology and the development of novel therapeutic strategies.

Given the critical importance of PCP signaling to both maintaining polarized epithelial tissue organization and promoting migration and convergent extension processes during development, the emerging role for aberrant PCP pathway activity in tumor malignancy should not be surprising. The engagement of dormant developmental processes to facilitate the aggressiveness of tumor cells is a common theme in cancer biology. Because the classic tissue-wide phenotypic depiction of PCP is lacking in the context

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