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Polarity proteins as regulators of cell junction complexes: Implications for breast cancer

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ABSTRACT

The epithelium of multicellular organisms possesses a well-defined architecture, referred to as polarity that coordinates the regulation of essential cell features. Polarity proteins are intimately linked to the protein complexes that make the tight, adherens and gap junctions; they contribute to the proper localization and assembly of these cell–cell junctions within cells and consequently to functional tissue organization. The establishment of cell–cell junctions and polarity are both implicated in the regulation of epithelial modifications in normal and cancer situations. Uncovering the mechanisms through which cell–cell junctions and epithelial polarization are established and how their interaction with the microenvironment directs cell and tissue organization has opened new venues for the development of cancer therapies. In this review, we focus on the breast epithelium to highlight how polarity and cell–cell junction proteins interact together in normal and cancerous contexts to regulate major cellular mechanisms such as migration. The impact of these proteins on epigenetic mechanisms responsible for resetting cells toward oncogenesis is discussed in light of increasing evidence that tissue polarity modulates chromatin function. Finally, we give an overview of recent breast cancer therapies that target proteins involved in cell–cell junctions.

Contents

1. Introduction

The epithelia constitute the majority of mammalian tissues, and are at the origin of 90% of human cancers. Epithelial differentiation and function depend on three major aspects: establishment of intercellular junctions and adhesion, basoapical polarity and proper mitotic spindle orientation (Dickinson et al., 2011). Cellular differentiation is characterized by a cell acquiring a defined structure that enables it to interact with other cells and with its microenvironment, including the stroma, hormones, growth factors and the extracellular matrix, to perform specific functions, as opposed to a stem cell that has no defined "identity"

Abbreviations: AJ, Adherens junction; Cx, Connexin; EMT, Epithelial to mesenchymal transition; GJ, Gap junction; GJIC, Gap junction intercellular communication; JAM, Junctional adhesion molecule; MDCK, Madin–Darby Canine Kidney Epithelial Cells; TJ, Tight junction; ZO, Zonula occludens; ZONAB, ZO-1 Nucleic Acid Binding Protein.

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and can give rise to various cell types. To attain a wide range of functions such as protection, secretion and absorption, epithelial cells form highly organized tissues characterized by the tight regulation of polarity and cell–cell junction complexes. Epithelial cell polarity is defined as the asymmetrical distribution of cell junction and polarity proteins. It contributes to the polarization of the epithelial tissue, which is characterized by the coordination of cell behavior in a two-dimensional sheet and the establishment of asymmetry within thousands of epithelial cells. Importantly, the formation of junction complexes at cell–cell contacts, better known as cell junctions, determines the architecture of the epithelium by mediating adhesion of cells to one another in an orderly manner, with tight junctions at the apex of cells (i.e., at the opposite cellular pole compared to the cellular pole in contact with the extracellular matrix) determining the limit between apical polarity and basolateral polarity. Cell junctions also mediate communication by allowing the passage of signals and metabolites between neighboring cells. Polarity and cell junction proteins act in concert whereby the same proteins that control polarity dictate the allocation of cell junction proteins. In addition, both types of proteins are classified as signaling hubs that regulate signal transduction pathways involved in normal and cancer cell functions as we will discuss in the context of this review. On the other hand, tissue architecture, which depends on proper cell–cell and cell–extracellular matrix interactions involving a reciprocal exchange of mechanical and biochemical stimuli (Hansen & Bissell, 2000), is altered in the early stages of cancer. Therefore, research efforts to decipher the mechanisms through which cell junctions and polarity proteins contribute to the acquisition and maintenance of normal tissue architecture are paramount.

1.1. Breast development and cancer

Being one of very few organs that continue to develop and differentiate late during the lifespan of an individual, the mammary gland is a good model to study how changes in the interaction between cells and their environment, as well as modulations in tissue architecture, might lead to tumor development. The mouse has long emerged as a primary animal model for the human breast development because both species have a number of similarities at the level of the structure and function of their mammary glands. The mouse mammary gland is a specialized organ that begins developing at day 10 of gestation with the formation of the mammary line (Watson & Khaled, 2008). At embryonic day 16, ductal branching morphogenesis begins once the mammary sprout reaches the fat pad, hence giving rise to the rudimentary ductal tree present at birth (Hens & Wysolmerski, 2005). During puberty, a second round of rapid expansion of the ductal epithelial cells takes place concurrent with ductal lumen formation (Foley et al., 2001). The full differentiation of the mammary gland occurs upon pregnancy, during which extensive proliferation and sprouting of the mature milk-producing alveoli occurs (Hens & Wysolmerski, 2005). These morphogenetic events are accompanied by cellular differentiation processes that result in specialized types of cells such as epithelial cells that form the ductal network, with adipocytes that constitute the fat pad in which the ductal network is embedded, vascular endothelial cells that make up the blood vessels, stromal cells that include fibroblasts and a variety of immune cells. There are two main types of epithelia in the mammary gland: the luminal epithelium that forms ducts and the secretory alveoli, and the basal epithelium that consists essentially of myoepithelial cells. Both luminal and myoepithelial cells harbor mammary stem cells that endow extensive renewing capacities to the mammary gland during remodeling. Indeed, these stem cells have great implications for the understanding of the mammary gland physiology, and most importantly, provide a new insight to recognize a potential origin of breast cancer (Visvader & Lindeman, 2011). The differentiation of the mammary epithelium encompasses the attachment of epithelial cells to the basement membrane (a specialized form of extracellular matrix), thus creating the basal pole and the formation of the lumen apically by sealing cell–cell contacts with tight junctions, which overall defines the basoapical polarity axis. Perturbations in mammary epithelial cell adhesion, communication and polarity could bring about one of the most common types of cancers in women worldwide. Breast cancer has become the most frequent carcinoma and the second most common cause of cancer-related mortality in women. Since 1999, incidence rates of in situ breast cancers have continued to increase in women below 50 years of age and have become stable in women aged 50 and older (Breen et al., 2011). Given such rates of incidence and mortality, a better understanding of the molecular mechanisms that ensure normal differentiation of the mammary gland is vital to unravel how breast cancer is initiated so that improved anticancer strategies can be devised. Normal differentiation at the tissue level requires establishment of a specific architecture, which is partly accomplished through cell junctions and polarity.

1.2. Cell junctions and polarity

Cell junctions are classified into tight junctions (TJ), adherens junctions (AJ), and gap junctions (GJ) (Fig. 1). These junctions consist of transmembrane proteins with intracellular domains that interact with partner signaling molecules, and extracellular domains that mediate the communication between neighboring cells. Cell junction complexes are asymmetrically localized as a result of the formation of the basoapical axis, characteristic of the polarized epithelium (Nelson, 2003). Formation of a basoapical polarity axis not only regulates the localization of cell junctions, but also modifies gene expression patterns via the interaction of junction and polarity proteins with genome remodeling factors.

Much of what is known about the mechanisms of basoapical polarity comes from studies in *Drosophila melanogaster* (Wodarz, 2005); these are being extended to mammals to define the pathways through which signals integrate and establish polarity during tissue morphogenesis (Macara, 2004). The investigation of polarity in *Drosophila* has characterized a highly conserved set of proteins referred to as polarity proteins and classified them into three functional groups: Crumbs, Par and Scribble that will be highlighted in the context of this review (Fig. 1).

Interestingly, cell adhesion, cell communication and polarity have long been correlated with a normal phenotype of epithelial cells; however, an emerging body of evidence has revealed that tumor cells also tend to adhere and communicate among each other and with other cell types. It is now established that coordinated communication via cell–cell contacts as well as cell polarization characterize invasive tumors since both of these features are essential for the migration and metastasis of cancer cells (Bravo-Cordero et al., 2012). This information implies that multicellular organization associated with cell junction formation and polarity should not only be gained from the context of normal differentiation but also in oncogenesis (Scheel & Weinberg, in press). Paradoxically, loss of tissue polarity is a precondition to tumorigenesis (Shin et al., 2006; Chandramouly et al., 2007). Therefore, the regulation of polarity is critical not only to normal differentiation but also to cancer initiation and progression. Further understanding of the biology of cell junction and polarity proteins and their associated pathways is essential for identifying potential biomarkers to improve detection and therapies of carcinomas.

1.2.1. Cell junctions have transcended their ascribed roles as structural cellular components

Although cell junction molecules serve to provide a structural continuum between cells, they are now perceived as signaling hubs integrating signals from the cell's surrounding to modulate cell function and often gene expression (Dbouk et al., 2009; Giepmans & Ijzendoorn, 2009). Cell junctions independently contribute to the maintenance of tissue morphology and homeostasis; nevertheless, they display overlapping localization and multiple interactions among each other.

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