Developmental Biology 401 (2015) 132–142

Contents lists available at ScienceDirect

Developmental Biology

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

The dystroglycan: Nestled in an adhesome during embryonic development

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ARTICLE INFO

Article history:
Received 17 April 2014
Received in revised form
23 June 2014
Accepted 8 July 2014
Available online 19 July 2014

Keywords:
Adhesome
Dystroglycan
Extracellular matrices
Development

ABSTRACT

Invertebrate and vertebrate development relies on complex processes that require many coordinated cell functions including cell adhesion, migration, proliferation and polarization. These processes depend on tissues and are spatio-temporally regulated by specific interactions between cells and between cells and the extracellular matrices. The dystroglycan, a transmembrane receptor that binds multiple extracellular matrix proteins, is expressed from oogenesis to organogenesis. There are increasing data suggesting that the axis, consisting of extracellular component–dystroglycan–cytoplasmic proteins, controls both the adhesion of cells to matrices as well as the transduction of signals coming from or directed to matrices. In this article, we review current advances leading to consider that the dystroglycan is a key protein nestled in an adhesome involved in mechanisms of cell adhesion during embryonic development.

Introduction

Embryogenesis depends largely on coordinated cell–cell and cell–extracellular matrix adhesions. For a long time, extracellular matrices (ECMs) were seen as stable structures to support the morphogenesis of tissues and organs. It now seems clear that ECMs are surprisingly dynamic and versatile and that they influence, through direct or indirect means, all steps of embryonic and adult life. ECMs are evolutionarily ancient structures, which probably appeared when the first communities of cells have emerged (for a review, Adams, 2013). ECMs are composed of heterogeneous networks of fibrillar and non-fibrillar components including collagens, laminins, fibronectin, nidogen, elastin, fibrilins, tenascin, proteoglycans and non-proteoglycan polysaccharides. These ECM components are secreted and assembled locally into organized networks that are present in invertebrate and vertebrate embryos. ECMs are dynamic structures of the cell environment, whose composition and spatial organization differ between species, developmental steps and tissues. In most species, ECM components act as a reservoir and a scaffold for growth factors, hormones and extracellular miRNAs (Edeleva and Shcherbata, 2013; Piccinini and Midwood, 2014). They also act to present growth factors to their receptors, to sense and transduce mechanical signals (Schiller and Fässler, 2013).

Conventionally, ECMs have been defined as including basement membranes (*basal laminae*) and interstitial matrices, which are less compact and more porous than basement membranes. Interstitial matrices are present between cells, are made by stromal cells, and are fibrillar. The structure of interstitial matrices depends on the nature of fibrils, the type and amount of proteoglycans. Interstitial matrices are found in loose and dense connective tissues such as cartilage, bone, and embryonic connective tissues. Basement membranes are sheet-like cell-adherent extracellular matrices that surround or underlie cells, tissues and organs. They are composed of independent networks of laminins and collagens that are tethered to nidogens and proteoglycans (Yurchenco and Patton, 2009). Basement membranes represent barriers limiting bacterial and viral offensive or infiltration of malignant cells between tissues. Alterations of basement membranes and interstitial matrices deregulate the behavior of cells and are often responsible for developmental disorders and various diseases (Lu et al., 2012).

ECMs components bind to cell surface receptors that are mainly transmembrane glycoproteins connecting them to cytoskeleton networks directly to actin or via cytoskeletal linkers. They provide links

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http://dx.doi.org/10.1016/j.ydbio.2014.07.006
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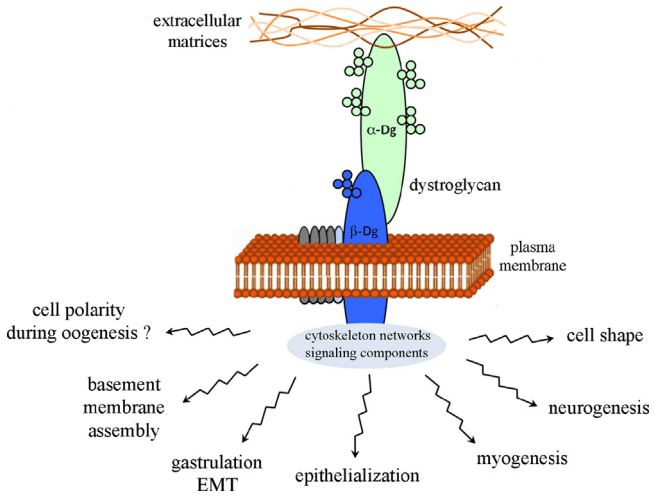

Fig. 1. The main functions of the dystroglycan adhesome during development. The components of extracellular matrices bind to α-Dg. This interaction results in the binding of the intracellular domain of β-Dg to cytoskeleton networks or signaling components. This consequently leads to several functions for the Dg adhesome according to species, tissues, organs and stages of embryonic development. EMT: epithelial-to-mesenchymal transition.

between ECMs and the underlying cytoskeleton leading to solid anchorages of cells, cytoskeletal rearrangements, co-regulations of growth factor activities and activations of signal transduction. They also provide direct or indirect controls of cellular activities such as adhesion, migration, differentiation, proliferation, and apoptosis. Furthermore, they are crucial for biochemical signals, which transit from the cell surface through the cytoplasm to the nucleus to activate or repress the transcription of genes. In turn, cells could modify and remodel ECMs by feedback-regulations and thereby control their extracellular environments. Although researches on the role of ECM receptors have been mainly focused on the α/β-heterodimeric transmembrane integrin proteins, the role of other receptors cannot be excluded as shown by more and more studies. It is in particular the case for the dystroglycan (Dg), a cell surface receptor for ECM components. For several years, various model organisms have been used to study ECM/Dg interactions in particular during adhesion processes. These include nematode worm, fruit fly, zebrafish, frog, chicken and mouse. They all contributed in various ways and significantly to our understanding of the functions of Dg as part of an adhesome during embryogenesis. This particular structure is a multi-molecular complex bringing together membrane receptors, adapter proteins, actin-associated proteins, kinases, phosphatases, G-proteins, Guanine nucleotide exchange factors (GEFs) and GTPase-activating proteins (GAPs). An adhesome provides interactive interfaces between ECMs, cellular scaffoldings and signaling machineries (Geiger and Yamada, 2011).

In this review, we will describe the Dg structure and its ligands and focus on Dg adhesive functions during embryonic development using data provided by genetic experiments, gain or loss-of-function and mutations (Fig. 1). However, the Dg is also involved in other processes outside of embryonic development, which will not be discussed here, such as hematopoiesis, virus particle entry and cancers. The latter are apparently associated with a loss of Dg affecting both cell adhesion and migration (Sgambato and Brancaccio, 2005).

Dystroglycan discovery, characterization and ligands

In 1987, biochemical studies from brains of embryonic chickens had led to the identification of a laminin-binding protein with a molecular mass of 120 kDa, called cranin (or LBP120) (Smalheiser and Schwartz, 1987). Later, searches for membrane molecules associated with dystrophin, the cytoskeletal protein that is defective in Duchenne's muscular dystrophy, resulted in the discovery of a novel complex of glycoproteins, labeled as the "dystrophin-glycoprotein complex (DGC)" (Ervasti et al., 1990). Subsequent cloning of these molecules revealed the complex to consist of multiple transmembrane molecules. The Dg has been identified as a glycan component of the complex and surprisingly, amino acid sequencing of the purified cranin demonstrated that it was identical to the Dg (Gee et al., 1993). Other members of the DGC include transmembrane proteins, sarcoglycans and sarcospan (Fig. 2). This complex, in turn, interacts with multiple cytoplasmic proteins, including dystrobrevin, syntrophin, utrophin, the latter two linking to F-actin.

The Dg gene is highly conserved between invertebrates and vertebrates. Protein sequence comparisons reveal that the Dg is a structurally distinct molecule, which belongs to none of previously identified families of cell adhesion molecules. It lacks strong homology with other proteins, although some similarity has been noted with immunoglobulin and cadherin-like domains (De Rosa et al., 2011). The Dg is a large glycoprotein generated by the translation from a single transcript. The precursor protein is subject to extensive co- and post-translational modification including proteolysis and extensive glycosylation resulting in two subunits, α and β, that interact noncovalently (Ibraghimov-Beskrovnaya et al., 1992). Interestingly, the *Caenorhabditis elegans* Dg appears not to be processed into separate α and β subunits upon maturation (Johnson et al., 2006). Also, the *Drosophila* Dg is encoded by a single gene, exists in differentially expressed splice versions, that lack the mucin-like domain and seems not to be cleaved (Deng et al., 2003; Schneider and Baumgartner, 2008).

The α-Dg subunit possesses two globular regions separated by a serine-threonine-rich mucin domain. The globular domains include potential sites for N-glycosylation, and the mucin region includes multiple consensus sites for O-linked glycosylation. This glycosylation is species specific, developmentally regulated and tissue specific leading to molecular mass of α-Dg varying between 120 and 200 kDa. The pattern of glycosylation dictates the specificity of ligand binding. The glycosylations of α-Dg allow binding to its ligands in a calcium-dependent manner through their "laminin G-like" (LG) modules, a protein motif present in many ECM proteins. The α-Dg has a complex and still not fully characterized pattern of glycosylation in its central mucin-type domain that is crucial since aberrant glycosylation of α-Dg is linked to diseases named dystroglycanopathies and to tumors (Muntoni et al., 2011; Moore and Winder, 2012). The α-Dg is known to bind laminins, agrin, neurexins, perlecan, pikachurin and biglycan (Fig. 2A; for a review: Sciandra et al., 2013). The major extracellular ligands for the Dg are members of the laminin family, which are major constituents of ECMs (for a review: Aumailley, 2013).

The β-Dg has a single domain spanning the plasma membrane and an amino-terminal extracellular domain that binds to the carboxy-terminal globular domain of α-Dg. The transmembrane domain of the β-Dg subunit is known to interact with sarcoglycans (α, β, γ and δ) and sarcospan. Their function is not fully understood. They form a sarcoglycan–sarcospan subcomplex that stabilizes the α-Dg association with β-Dg at the cell surface (for a review: Marshall et al., 2013). The cytoplasmic tail of β-Dg interacts with the proteins dystrophin, utrophin, syntrophins and α-dystrobrevin, thereby to F-actin (for a review: Cohn and Campbell, 2000). By co-immunoprecipitation and gel overlay assays, the dystrophin containing the WW domain and two putative Ca^{++}-binding EF-hand motifs were shown to interact with the β-Dg cytoplasmic domain (Rentschler et al., 1999). Thus, the Dg-dystrophin and Dg-utrophin complexes form cell adhesion