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Review

Configuring a robust nervous system with Fat cadherins

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ABSTRACT

Atypical Fat cadherins represent a small but versatile group of signaling molecules that influence proliferation and tissue polarity. With huge extracellular domains and intracellular domains harboring many independent protein interaction sites, Fat cadherins are poised to translate local cell adhesion events into a variety of cell behaviors. The need for such global coordination is particularly prominent in the nervous system, where millions of morphologically diverse neurons are organized into functional networks. As we learn more about their biological functions and molecular properties, increasing evidence suggests that Fat cadherins mediate contact-induced changes that ultimately impose a structure to developing neuronal circuits.

Contents

1. Introduction

Cadherins constitute a superfamily of transmembrane proteins with varying numbers of calcium-binding cadherin domains that enable cell–cell interactions, in some cases resulting in the formation of stable junctions and in other cases activation of signaling pathways that impact the cytoskeleton, gene expression, and the cell cycle [1]. Initially described as cell adhesion molecules, cadherins vary widely in structure and fall into different subfamilies based on the presence of additional protein interaction domains extracellularly, the number of transmembrane domains, and the composition of their intracellular domains [2]. The classical cadherins, for instance, generally have five cadherin repeats and are characterized by the presence of catenin binding sites in the intracellular domain, consistent with their well-defined role in cell adhesion. All other molecules bearing cadherin domains are loosely defined as "protocadherins", a group that comprises many additional subgroups based on their sequences and chromosome organization [3]. For example, the genes that encode the α–, β–, and γ-protocadherins are clustered in three distinct arrays in the genome, each of which contains several variable exons that are driven by their own promoters. Selection of a certain promoter and hence a certain exon seems to be achieved by differential promoter methylation and allows for the production of a variety of single transmembrane proteins with six cadherin domains that provides

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neuronal individuality [4]. The atypical Fat cadherins, on the other hand, stand out for their enormous size, up to 500–600 kDa, largely due to the presence of a huge extracellular domain containing 32–34 cadherin repeats, 1–2 laminin A–G and 4–5 EGF repeats [5,6]. Additionally, Fat cadherins have cytoplasmic domains that vary within the family and can recruit many different intracellular effectors, including transcription factors and actin regulators.

Cadherins play a particularly prominent role in the nervous system, which hosts a large population of diverse cell types that must be organized into coherent networks. Whereas classic cadherins and the clustered protocadherins direct neural circuit assembly through their effects on cell-type recognition and self-recognition [7,8], the role of Fat cadherins in the nervous system is less clear. In fact, Fat cadherins are present even in the simplest multicellular animals, predating the expansion of protocadherins in animals with more complex nervous systems [9]. Other cadherins have been proposed to be derivatives of the Fat cadherins, arising by steady loss of cadherin repeats and acquisition of new cytoplasmic domains, raising the possibility that Fat cadherins originally enabled basic cell–cell interactions that were adapted to new contexts in the nervous system, as witnessed by the evolution of subfamilies with more dedicated roles. With only 2–4 family members in any species and no evidence for the extensive diversity of the clustered protocadherins [7], Fat cadherins are not equipped to provide much in the way of specificity during cell–cell interactions. Instead, individual Fat cadherins stand out as versatile molecules that can influence cell adhesion, morphology, and proliferation via a range of extracellular interactions and intracellular effectors. Although it remains unclear whether there is one unifying function, emerging evidence suggests that Fat cadherins coordinate complex changes in cell morphology with the surrounding environment, thereby imposing a tissue-level order not only in epithelia such as the fly wing but also within developing circuits of the vertebrate nervous system.

1.1. Basic features of the fat cadherins

What is best known about Fat function comes from studies in *Drosophila*, which have one *fat* (*ft*) gene and one *fat-like* gene (a.k.a *fat2* or *kugelei*). Analysis of these two huge atypical cadherins has defined two core functions: cell proliferation and tissue polarity [10]. Together with its Dachsous ligand, Ft appears to regulate proliferation and polarity through different intracellular pathways (Fig. 1A). Despite obvious structural and functional homologies to Ft, Fat-like acts through a different ligand and different effectors. Nonetheless, both molecules share the ability to mediate local cell–cell interactions and thereby coordinate cell behavior across tissues.

Ft was originally described as a tumor suppressor gene, as loss of function mutations led to increased cell proliferation and thus abnormal enlargement of larval imaginal discs [11], hence its name. In *Drosophila*, the Ft ligand is another unusually large cadherin, Dachsous (Ds) [12], which is also involved in cell proliferation [13]. Later findings positioned Ft and Ds as upstream regulators of the Hippo pathway [14–19], which controls organ size by regulating transcription of pro-proliferation and cell death genes [20]. The Hippo pathway involves a series of phosphorylation events where Hippo (Hpo) and Salvador (Sav) form a kinase complex that phosphorylates and activates the kinase complex formed by Warts (Wts) and Mob-as-tumor-suppressor (Mats). One effector of this kinase cascade is the transcriptional co-activator Yorkie (Yki), whose Hippo-dependent phosphorylation prevents it from entering the nucleus and, therefore, acting as a transcriptional co-activator [20,21]. Ft-Ds has been proposed to serve as a receptor-ligand pair that regulates Hippo signaling, culminating in activation of the Hpo-Wts kinase cascade and inhibition of Yki by regulating components such as Expanded and Dachs [22].

In addition to its effects on proliferation, Ft also plays a key role in the polarization of cellular structures. Many cells acquire asymmetric morphologies that must be organized across an entire organ, a feature known as tissue polarity. Two classic examples are the *Drosophila* wing, where cells uniformly point trichomes distally, and the compound eye, where units of photoreceptors are oriented towards the equator. Genetic screens for defects in each of these tissues uncovered two molecular systems that control both the local organization of polarized cells within the epithelium ("planar cell polarity") and the long-range organization of this polarity across the epithelium ("tissue polarity") [23,24]. The orientation of neighboring cells depends on the "core" planar cell polarity (PCP) signaling pathway, which comprises Frizzled (Fz), Disheveled, Prickle, Van Gogh, Diego and Flamingo [23,25]. Ft participates in a second, less understood system that somehow coordinates more global features of polarity. As in cell proliferation, Ft works together with Ds to control tissue polarity, but in this case not strictly through the Hippo pathway. Although there is strong evidence that cells rely on systematic differences in Ft-Ds interactions to sense their position and hence orientation within an organ, exactly how changes in cell shape are brought about remains poorly understood.

In both the fly wing and eye, tissue polarity depends on gradients of Ft and Ds activity (Fig. 1B). In the wing, a Ft-Ds activity gradient results in the asymmetric distribution of the intracellular myosin Dachs and hence formation of distally pointing trichomes [26]. Additional positional information is provided by the Golgi kinase Four-jointed (Fj), which modulates the strength of the Ft/Ds interaction by phosphorylation of their extracellular domains [27]. Ft is uniformly expressed, but Ds and Fj are both expressed in gradients. Thus, heterotypic interactions with Ds result in graded activity of Ft, ultimately read out as asymmetric membrane localization of Dachs. Ft and Ds also influence each other's localization, possibly transmitting asymmetric distribution within one cell to its neighbor.

Gradients of Ft and Ds activity also organize multicellular structures, such as the ommatidia of the eye. Each ommatidium consists of eight photoreceptors, seven of which are arranged into trapezoids that point away from the equator of the eye, with ommatidia in the dorsal half pointing up and those in the ventral half pointing down. The Ft/Ds system specifies the identity of the photoreceptor at the tip of the trapezoid and hence its orientation [28]. Thus, in both cases, gradients of Ft/Ds activity lead to tissue-wide changes in cell behavior. Importantly, Ft also has non-autonomous effects and can influence cells at a distance, though it is unclear whether this is by serial propagation of local changes in protein distribution or instead through production of a long-range signaling molecule [29].

Ft appears to convey polarity information through a variety of downstream effectors that enable diverse cellular effects. For instance, distinct domains within the Ft cytoplasmic domain are required for proliferation or for planar polarity [30]. There is little consensus regarding the nature of the planar polarity effectors. In some contexts, different levels of Ft/Ds interactions influence protein distribution and perhaps establish an axis for the core PCP pathway. This is clearest in the wing, where the Ds/Ft/Fj module biases the asymmetric distribution of Fz in wing cells [31]. This may be through direct effects on the cytoskeleton, for example by orienting microtubules and hence the movement of vesicles carrying cargo such as Fz [32]. However, the relationship between these two systems remains controversial and may depend on context [29,33,34]. For example, in the eye, Ft/Ds interactions regulate the level of Fz signaling and hence the identity of the precursor closer to the equator of the eye [28], but these effects depend on regulation of gene expression by the transcriptional co-repressor Atrophin (Atro), which binds to the Fat intracellular domain (ICD)