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Secret handshakes: cell–cell interactions and cellular mimics

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Cell–cell junctions, acting as 'secret handshakes', mediate cell–cell interactions and make multicellularity possible. Work over the previous century illuminated key players comprising these junctions including the cadherin superfamily, nectins, CAMs, connexins, notch/delta, lectins, and eph/Ephrins. Recent work has focused on elucidating how interactions between these complex and often contradictory cues can ultimately give rise to large-scale organization in tissues. This effort, in turn, has enabled bioengineering advances such as cell–mimetic interfaces that allow us to better probe junction biology and to develop new biomaterials. This review details exciting, recent developments in these areas as well as providing both historical context and a discussion of some topical challenges and opportunities for the future.

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Introduction

Underlying complex, coordinated, multicellular behaviors is a key cellular decision made at each physical contact. For each interaction, cells classify the contacting object either as 'not-cell' (e.g. extracellular matrix [ECM]) or 'cell' which is further classified based on the cell type (e.g. epithelia vs. muscle). The type of classification dictates subsequent cellular behaviors (e.g. focal adhesion formation with ECM via integrins vs. cell–cell adhesion via cadherins or other junctional proteins), and the net result of those decisions across a tissue affect the spatial organization and function of cells, the establishment of homeostasis, healing of an injury, or even the invasion and metastasis of cancer cells. In this review, we focus on juxtracrine interactions that arise specifically via mechanical contacts between cells. After providing historical context and reviewing recent, biological findings, we discuss how our growing understanding of cell–cell adhesion and recognition is being parlayed into powerful new tools to study and manipulate cellular behaviors.

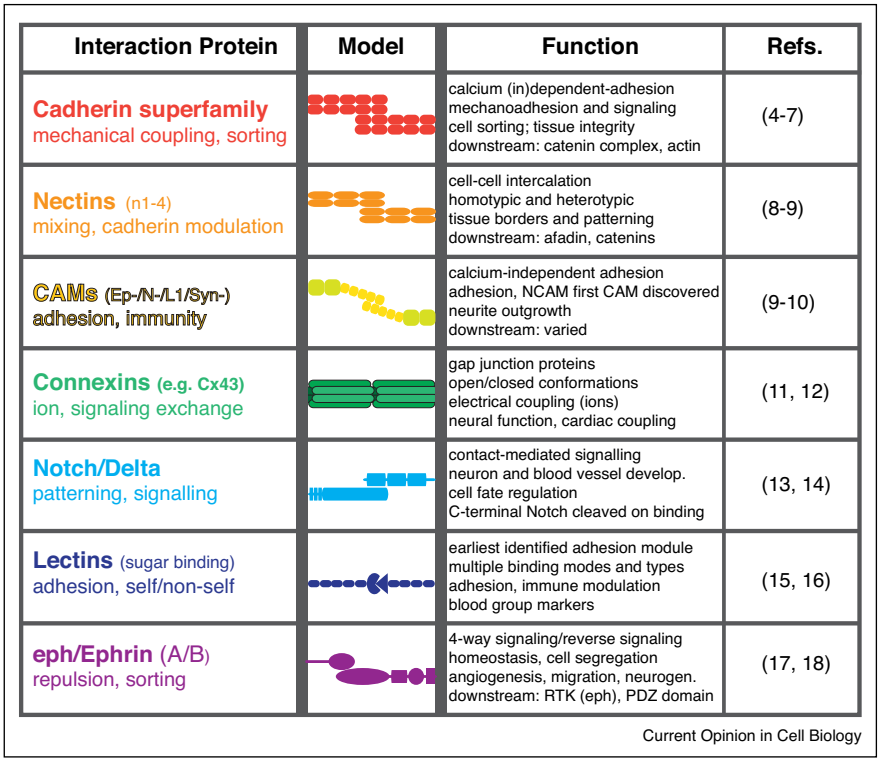
From locks and keys to secret handshakes

While questions of how cells recognize and attach to other cells have played a central role in Biology for over a century, the players involved remained unknown until relatively recently. Despite the first experiments demonstrating species-specific cell–cell recognition and adhesion performed by Wilson in 1907 [1], it would not be until 1977 that the first vertebrate cell–cell adhesion protein, N-CAM, was identified (Edelman *et al.* [2]), and not until 1981 that the cadherins were discovered (Takeichi *et al.* [3]). Since then, the list of players implicated in cell–cell recognition and adhesion has grown to include the cadherin superfamily comprising classical, atypical-cadherin and proto-cadherin [4–7], nectins [8,9], CAMs [9,10], Connexins [11,12], Notch/Delta [13,14], Lectins [15,16], and eph/Ephrin [17,18••] (Figure 1). Such a rich palette of adhesion proteins has the potential to provide radically different effects upon cell–cell contact, from pure repulsion to pure adhesion and everything in between.

The earliest models for how cell–cell recognition occurs relied on the 'Lock-and-Key' framework proposed by Fischer (1897) and further developed by Ehrlich (1900) in which cell recognition depended on unique ligand/receptor pairs [19]. Holtfreter and Townes [20] expanded on this to propose that cell-type specific adhesion molecules could mediate adhesion and tissue patterning in a process called 'Selective Affinity'. Steinberg's 'Differential Adhesion' hypothesis (1965) reflected an alternative framework requiring only differential relative adhesion between cell types [21]. In essence, Selective Affinity posits that cell types A and B must have different adhesion proteins in order to separate into unique tissues, while Differential Adhesion posits that cell types A and B can have the same adhesion protein but will sort out uniquely so long as the level of the adhesive protein is different in a cell type-specific manner.

Since these models were proposed, a sea change has occurred in terms of how we think about of cell–cell recognition, adhesion and tissue sorting mechanisms. As none of the original models were correct in all

Figure 1



Summary of key cell–cell interaction proteins.

particulars, we have had to broaden our understanding of what recognition and adhesion mean. For instance, we now know that: firstly, one adhesion protein can support both heterotypic and homotypic interactions (e.g. cadherins) [22••,23]; secondly, different recognition and adhesion modules can be multiplexed to guide cellular responses (e.g. cadherins and ephrins) [18••,24]; and thirdly, even the geometry of how these adhesion proteins are presented can affect how they are interpreted (e.g. 3D presentation of cadherin, and junction size and cell shape in Notch signaling) [25••,26••]. In light of this, our modern framework of cell–cell recognition and adhesion includes elements of the Lock-and-Key, Selective Affinity, Differential Adhesion, and more recent Differential Interfacial Tension models [27]. This new synthesis reflects the fact that cell–cell contacts are complex, multivariable systems where the type, level, cross-interactions, and spatial presentation of the cell–cell interaction proteins are integrated to determine the adhesion and recognition response — akin to a cellular 'secret handshake'.

The cell–cell adhesome: complementary and contradictory cues

A given cell type can be characterized by the complement of proteins in the cell–cell adhesome (see Figure 1). As each protein modulates downstream effectors in unique ways, combinatorial presentation of cell–cell adhesion proteins can result in complex interactions between cells with different phenotypic outcomes beyond that of simple adhesion or repulsion [18••,22••,28,29••]. Even different members of the same family of adhesion proteins expressed in the same cells can contribute different effects. For instance, recent work in epithelial cells expressing both E-cadherin and P-cadherin showed that P-cadherin levels tracked the absolute level of intercellular tension, whereas E-cadherin levels responded to the rate of change of intercellular tension [28]. Hence the co-presentation of multiple recognition and adhesion proteins can have profound effects on tissue properties and organization. The following case studies highlight this in the specific contexts of complementary and contradictory interactions at the cell–cell junction.

Recent work by Katsunuma *et al.* [29••] demonstrates how the presentation of complementary adhesive proteins plays out in the olfactory epithelium due to the contributions of two different cadherins (E-cadherin and N-cadherin) and two different nectins (nectins 2 and 3). The olfactory epithelium is a monolayer of supporting epithelial cells studded at regular intervals with olfactory sensory cells (Figure 2a). There are fewer sensory cells than support cells and, *in vivo*, the olfactory epithelium takes on the appearance of a regularly spaced, hexagonal array