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Tissue Structure: A CIVICs Lesson for Adipocytes

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A new study upends the clear distinction between cell–cell adhesion and cell–matrix adhesion by showing that type IV collagen is essential for inter-adipocyte adhesion in the *Drosophila* fat body.

Multicellular organisms have a fascinating array of tissue patterns whose organization requires a combination of intercellular adhesion and adhesion between cells and their extracellular matrices (ECMs). Cells use cell–cell adhesion molecules like cadherins to recognize that they are from the same tissue, form cell–cell junctions, and establish polarized domains [1]. Cells also form adhesions with the ECM that allow them to sense the mechanical properties of their environment, migrate, and receive polarity and growth signals [2]. Cell–cell and cell–ECM adhesions have traditionally been considered discrete types of contacts. In this issue of *Current Biology*, Pastor-Pareja and colleagues [3] blur the lines between these phenomena by introducing an essential role for the ECM protein type IV collagen (Col IV) in mediating cell–cell adhesion in the *Drosophila* fat body. The authors go on to link these ECM-based cell–cell adhesions to pro-growth signaling, suggesting that they play an important role in how cells monitor the growth needs of their tissue.

The fat body is the major metabolic center of the fly. In addition to storing lipids, fat body adipocytes also serve a liver-like function, secreting growth factors and metabolites into the fly's open circulatory system — the hemolymph — for use by tissues throughout the animal [4]. The fat body also regulates organismal growth by responding to hormonal and nutritional signals. The ability to respond quickly to these signals is thought to be, in part, a product of the fat body's dispersed organization, as it stretches throughout the body for maximal exposure to the hemolymph [4]. The fat body is composed of a single layer of adipocytes that are packed into a hexagonal honeycomb-like pattern, an organization that is typically associated with epithelial tissues. However, the fat body is a mesenchymal tissue, and it had been unclear how its compact organization is achieved.

Pastor-Pareja had previously shown that the fat body is also the main site for Col IV synthesis in the developing larva [5]. The majority of the Col IV produced by the fat body is secreted into the hemolymph and then assembled into dense, sheet-like ECMs called basement membranes (BMs), which surround many organs, including the fat body itself. In the new study, the authors looked more closely at the organization of Col IV in the fat body and noticed that, in addition to its BM localization, Col IV assembles into thick, irregularly shaped plaques that dot the adipocytes' cell–cell interfaces (Figure 1). They subsequently named these structures Col IV intercellular concentrations (CIVICs).

Identification of these CIVICs raised the intriguing possibility that Col IV might play a non-BM role, moonlighting as an intercellular adhesion molecule. Indeed, depletion of Col IV from the fat body caused the cells to round up and lose their hexagonal packing, creating gaps within the monolayer. This intercellular adhesion function is unique to Col IV among the BM proteins. Although CIVICs contain all four major BM proteins, the loss of laminin, perlecan, or nidogen disrupted the fat body's BM without affecting intercellular adhesion. Together, these results indicate that the population of Col IV contained within the CIVICs plays a key role in inter-adipocyte adhesion that is distinct from its role in the BM.

To determine how the CIVICs mediate cell–cell contact, the authors investigated two classes of receptors that have the potential to bind Col IV. Integrins are dimeric transmembrane receptors important for forming cell–ECM attachments called focal adhesions [6], and syndecan is a transmembrane heparan sulfate proteoglycan that can act as a co-receptor with integrins [7]. Reducing the levels of integrins or syndecan disrupted cell–cell contacts in a manner similar to the loss of Col IV, providing further evidence that fat body cells repurpose cell–ECM adhesion machinery for intercellular adhesion. The most striking images in the paper show that several focal adhesion proteins are highly concentrated along the CIVICs, demonstrating that a mature integrin-based adhesion forms at these locations. Additionally, overexpressing integrins or syndecan led to larger CIVICs, suggesting that receptor capture of Col IV mediates the formation of these structures. It remains unclear, however, how the CIVICs ultimately obtain their thick, irregular shapes and distribution across the tissue.

The identification of CIVICs also allowed the authors to ask a broader question — does the tight hexagonal packing of adipocytes play a role in fat body physiology? Loss of CIVICs or their receptors caused a dramatic decrease in cell size, suggesting CIVICs might regulate adipocyte growth. As the fat body can respond to the changing energy needs of the organism through either growth or autophagy [8], the authors explored whether the shrinking cells were a product of increased autophagy. Indeed, cells without CIVICs or their receptors had increased levels of autophagy markers, arguing that the CIVICs may play an important role in pro-growth and/or anti-autophagic signaling.

Phosphatidylinositol 3-kinase (PI3K)–Akt signaling is an important regulator of the adipocytes' decision either to grow or to undergo autophagy [8,9]. The authors reasoned that CIVICs might activate this pathway to prevent autophagy under

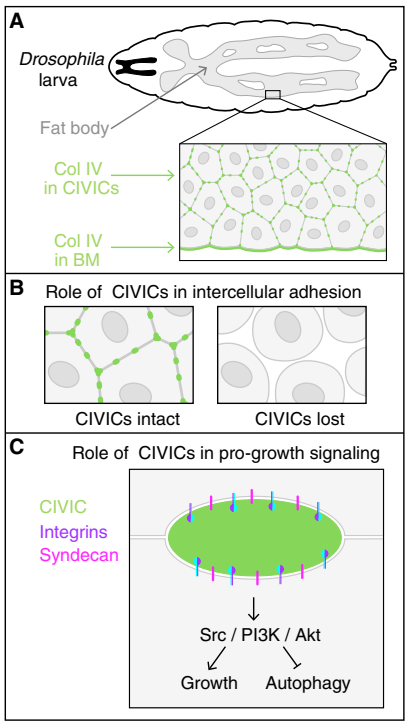

Figure 1. Role of CIVICs in intercellular adhesion and pro-growth signaling.
(A) Illustration showing the position of the fat body in a *Drosophila* larva. The zoomed-in image highlights the localization of type IV collagen both within the basement membrane (BM) extracellular matrix that surrounds the organ, and in plaques in between the cells that the authors have named CIVICs. (B) When CIVICs are lost, fat body cells round up and lose their characteristic hexagonal packing, revealing a role for CIVICs in intercellular adhesion. (C) Fat body cells interact with CIVICs through integrins and syndecan. Signaling downstream of these receptors appears to promote growth and inhibit autophagy.

normal conditions. To link Akt to CIVICs, the authors focused on the kinase Src, which is activated at integrin-based adhesions and functions upstream of Akt [10,11]. They observed that the activated form of Src was enriched at cell–cell interfaces, that Src activity depended on intact CIVICs, and that loss of Src induced autophagy. To further probe the role of this pathway, the authors overexpressed PI3K under conditions in which CIVICs are lost. This manipulation rescued the autophagy defect even though intercellular adhesion was not restored, demonstrating that CIVICs signal upstream of PI3K.

This new work by Pastor-Pareja and colleagues [3] suggests that we should expand our perceptions of the roles BM proteins play in organizing tissues. The BM proteins Col IV and laminin arose with multicellularity and are thought to be part of the 'glue' that allowed cells to organize into tissues [12]. Recent work in several systems has shown that BM proteins can form structures other than simple sheets, such as fibrils and loose networks [12–14]. A recent evolutionary investigation found that, in several phyla of marine invertebrates, Col IV is exclusively found in a dispersed form, with no discernable BMs present [12]. Pastor-Pareja and colleagues note that we lack a mechanistic understanding of how many tissues are held together, and this work may motivate the study of a whole new class of intercellular BM-based adhesion complexes. It will be exciting to see what keen observation of other tissues reveals about unconventional uses of BM proteins.

The focal adhesion-like structures formed at the CIVICs also suggest that there is more to learn about mechanical forces in the fat body. In a traditional integrin-based adhesion, the accumulation of focal adhesion proteins is often a readout for force-induced maturation of the adhesion site [15]. If this model holds for the CIVICs, what is the source of the applied force? Do adipocytes use actomyosin contraction to pull on these junctions? Does the flow of the secreted molecules between the adipocytes apply an external force to the CIVICs? Or, as the authors speculate, does the growth of the tissue apply pressure to these sites? Any one of these scenarios would provide insight into the role mechanical signaling plays in fat body physiology.

Finally, the beautiful electron and fluorescence microscopy in this paper highlight how looking closely at a tissue can generate unexpected insights. The identification of CIVICs advances our understanding of the fat body's structure, but it also raises new questions about how the thick profile and irregular distribution of these structures relate to this tissue's function. As a professional secretory organ, the fat body produces a variety of proteins that need to pass between the cell–cell junctions and diffuse into the hemolymph. Given that the majority of the Col IV produced by the fat body is also bound for the hemolymph, this ~400 nm long, rope-like protein poses a particular challenge. It is tempting to speculate that CIVICs might provide a means to link cells together into a tissue while still providing sufficient space for bulky secreted molecules to flow freely between the cells. It is interesting to note, however, that the fat body adipocytes also express traditional cell–cell adhesion molecules like DE-cadherin [16]. Integrin- and cadherin-mediated signaling have a complex relationship in development, but much of what we know about their intersection comes from *in vitro* studies [17]. Further study of CIVICs within the fat body may shed light on how multiple types of adhesions can be integrated to best serve the function of a given tissue *in vivo*.

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Social Behaviour: The Personalities of Groups

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A new study on stickleback provides a framework for understanding how the behaviour of individuals in groups, and the structure and movements of groups themselves, can be predicted from the personalities of individual group members.

Managers, judges or heads of department are well aware that different teams, juries or hiring committees differ substantially in their behaviour from one group to the next. However, predicting how groups of individuals will function together, when each individual has their own personality, opinions and desires is particularly challenging. This problem has also proved difficult for behavioural ecologists. It is well established that individual animals differ consistently in their behaviour [1,2]. But many species live in complex social environments, and it is far from clear how the heterogeneous make-up of groups of individuals with different personality types influences groups' collective behaviour. For example, do individuals with different personalities occupy different roles or different spatial positions in groups? How does a group's make-up influence how the group moves or how it is structured? And what are the functional consequences for individuals belonging to groups with others of similar or different personalities? More generally, it has been unclear how to develop and test a mechanistic framework that could help predict how individuals with different personalities will behave in groups. In this issue of *Current Biology*, Jolle Jolles and colleagues [3] tackle this problem using stickleback, and uncover how different group structures, leadership roles, movement patterns and foraging dynamics emerge when groups are composed of individuals with different personalities. Their comprehensive approach shows for the first time how the properties of groups can be predicted from the personality types of the constituent individuals.

Social environments are likely to maintain the diversity of personality types in populations. One reason for this is that frequency-dependent selection should act to maintain different behavioural phenotypes, as individuals with different personalities stand to gain benefits from associating with different types of individuals [4–6]. For example, less explorative individuals may benefit from associating with, and thereby scrounging information from, more explorative individuals, while more explorative individuals may benefit from the presence of less explorative individuals because the risk of predation is reduced in larger groups. However, many groups, such as bird flocks and fish schools, are characterised by fission–fusion dynamics, where group membership changes regularly [7]. Owing to the standing diversity of differences between individuals' behaviour, groups can therefore be composed of individuals with a multitude of different behavioural phenotypes [8]. There have been numerous attempts to predict how the behaviour of groups may depend on the personalities of their constituent group members, but this has yielded mixed results, especially in groups larger than pairs of individuals [9]. Sometimes the behaviour of individuals in groups can be predicted from how individuals behave on their own [10], whilst in other cases, it is unclear whether personalities are lost, or simply become undetectable in social settings [11].

The problem with understanding how individuals with different personalities will behave in groups stems from the complex web of factors that could influence an individual's behaviour in social environments. First, an individual's behavioural phenotype can be composed of multiple axes of behavioural variation [12]. For example, individuals may differ in how 'explorative' they are, but may also differ in their degree of 'sociability'. Importantly, these two axes may not necessarily be tightly coupled and therefore may be affected by the social environment in different ways. Second, which particular individuals an animal associates with, and thereby the relative