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Why do receptor–ligand bonds in cell adhesion cluster into discrete focal-adhesion sites?

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ABSTRACT

Cell adhesion often exhibits the clustering of the receptor–ligand bonds into discrete focal-adhesion sites near the contact edge, thus resembling a rosette shape or a contracting membrane anchored by a small number of peripheral forces. The ligands on the extracellular matrix are immobile, and the receptors in the cell plasma membrane consist of two types: high-affinity integrins (that bond to the substrate ligands and are immobile) and low-affinity integrins (that are mobile and not bonded to the ligands). Thus the adhesion energy density is proportional to the high-affinity integrin density. This paper provides a mechanistic explanation for the clustering/assembling of the receptor–ligand bonds from two main points: (1) the cellular contractile force leads to the density evolution of these two types of integrins, and results into a large high-affinity integrin density near the contact edge and (2) the front of a propagating crack into a decreasing toughness field will be unstable and wavy. From this fracture mechanics perspective, the chemo-mechanical equilibrium is reached when a small number of patches with large receptor–ligand bond density are anticipated to form at the cell periphery, as opposed to a uniform distribution of bonds on the entire interface. Cohesive fracture simulations show that the de-adhesion force can be significantly enhanced by this nonuniform bond density field, but the de-adhesion force anisotropy due to the substrate elastic anisotropy is significantly reduced.

1. Introduction

Bio-adhesive contacts have motivated a variety of biomimetic investigations mainly because the biological structures exhibit adhesion properties that are surprisingly high, low, or tunable in contrast to engineering structures. The fundamental analysis of adhesive contact has been well established in a fracture mechanics framework (Johnson, 1997). From the linear elastic fracture mechanics, the contact size is determined by balancing the energy release rate and the density of fracture energy (or adhesion energy). Nonlinear fracture analysis can also be found by the cohesive interface approach for

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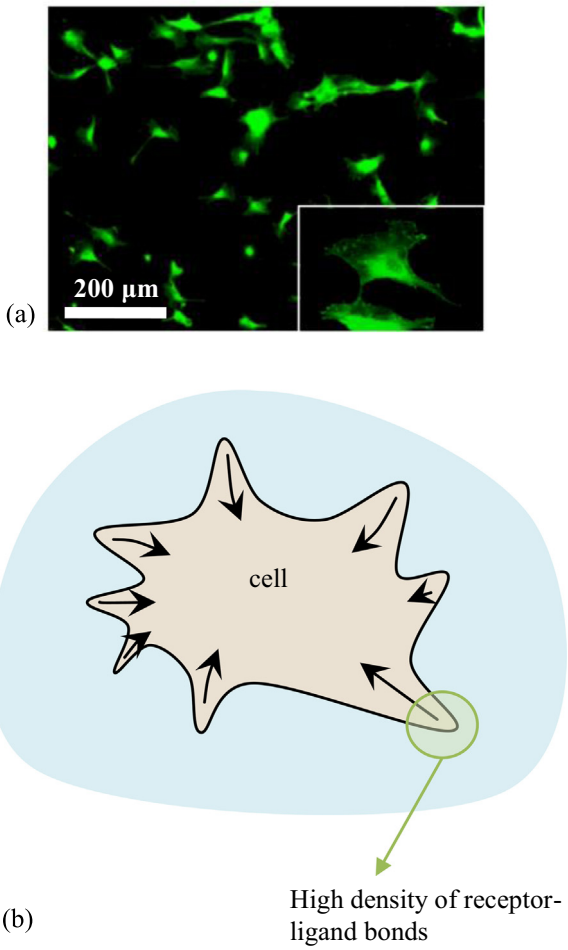

Fig. 1. (a) Focal adhesion of human aortic endothelial cells (HAECs) on a stainless steel substrate, as shown by the immunofluorescent staining image (Huang et al., 2015). (b) Schematic illustration of the clustering of receptor–ligand bonds into discrete focal-adhesion sites at the contact periphery.

applications in soft material adhesion or hard materials at nanoscales. The extraordinary adhesion force in fibrillar structures (such as gecko toes which has a hierarchical toe–lamellae–spatula structure with the spatula size on the order of submicrometers) is achieved mainly from the following findings: (1) the fibrillar structure can lead to a high ratio of true to nominal contact areas because of the additional compliance of these fibers; (2) the smallest scale, being the spatula in gecko adhesion, lies in the cohesive crack limit so that the de-adhesion force becomes higher than that if lying instead in the linear fracture mechanics limit; and (3) releasable adhesion can be realized either by elastic anisotropy of the substrate or due to the analogy to a peeling test that exhibits a dependence of applied energy release rate on the spatula–substrate attack angle and the peeling direction (Autumn et al., 2000; Gao et al., 2003; Yao and Gao, 2006; Gao and Bower, 2006; Chen and Gao, 2007; Ji and Gao, 2010; Zhang et al., 2013; Liu and Gao, 2015). Artificial miniature structures also design fibers with "mushroom" tip shapes so as to reduce the stress concentration at the contact edge, so that the de-adhesion force can be improved even when the adhesive contact problem falls in the linear elastic fracture mechanics limit (Spuskanyuk et al., 2008; Heepe and Gorb, 2014; Liu et al., 2015a, 2015b).

In contrast to the structural viewpoint in the above examples, there is a multitude of bio-adhesive contacts that achieve high adhesion force by *chemo-mechanical processes*, with cell adhesion being the quintessential example (Freund and Lin, 2004; Deshpande et al., 2006, 2007, 2008; Lin and Freund, 2008; Maloney et al., 2008; Pathak et al., 2008, 2011; Qian et al., 2009; Wang and Gao, 2010; Gao et al., 2011; Gao, 2014; He et al., 2014; Liu et al., 2015). As shown by the fluorescent staining image in Fig. 1(a) (Huang et al., 2015), the long-chain molecular receptor–ligand bonds in the cell adhesion often cluster into a small number of focal-adhesion sites. The adhered cells resemble rosette structures or stretched membranes anchored by a small number of edge forces as schematically shown in Fig. 1(b). The cell interior has a low density of receptor–ligand bonds. The ligands are immobile on the extracellular matrix (ECM). Integrins in the cell membrane are binding proteins that connect to the ligands outside the cell. There are two conformational states, i.e., a low affinity (or bent) state that does not interact with ligand molecules on the ECM, and a straight state with a high affinity to the ligands. The low affinity integrins are mobile within the plasma membrane, and the high affinity ones are immobile, as schematically shown in Fig. 2.