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Review

# Investigating biomolecular recognition at the cell surface using atomic force microscopy

Congzhou Wang, Vamsi K. Yadavalli*

*Department of Chemical and Life Science Engineering, Virginia Commonwealth University, Richmond, VA 23284, USA*

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ABSTRACT

Probing the interaction forces that drive biomolecular recognition on cell surfaces is essential for understanding diverse biological processes. Force spectroscopy has been a widely used dynamic analytical technique, allowing measurement of such interactions at the molecular and cellular level. The capabilities of working under near physiological environments, combined with excellent force and lateral resolution make atomic force microscopy (AFM)-based force spectroscopy a powerful approach to measure biomolecular interaction forces not only on non-biological substrates, but also on soft, dynamic cell surfaces. Over the last few years, AFM-based force spectroscopy has provided biophysical insight into how biomolecules on cell surfaces interact with each other and induce relevant biological processes. In this review, we focus on describing the technique of force spectroscopy using the AFM, specifically in the context of probing cell surfaces. We summarize recent progress in understanding the recognition and interactions between macromolecules that may be found at cell surfaces from a force spectroscopy perspective. We further discuss the challenges and future prospects of the application of this versatile technique.

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* Corresponding author. Tel.: +1 804 828 0587.
*E-mail address:* vyadavalli@vcu.edu (V.K. Yadavalli).

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## 1. Introduction

Biomolecular interactions play important roles in many biological and physiological processes (Hinterdorfer and Dufrene, 2006). Specific recognition processes between macromolecules on cell surfaces are essential for diverse cellular functions including embryonic development, signal transduction, immune response, cell adhesion, and tissue assembly (Bertozzi and Kiessling, 2001; Bustamante et al., 2004; Sheetz, 2001; Vogel and Sheetz, 2006). Recognition events on cell surfaces typically involve complex interactions between molecules such as membrane receptor proteins and ligands, carbohydrates and lectins, antigens and antibodies, and cell adhesion molecules (CAMs) and the extracellular matrix (ECM) (Fig. 1) (Kienberger et al., 2006; Mrksich, 2002; Wehrle-Haller and Imhof, 2002). For instance, membrane receptor proteins serve as mediators to transmit the biological signals between the cytoplasm and the extracellular environment, as realized *via* interactions with their specific ligands (Antonova et al., 2001; Jefford and Dubreuil, 2000; Thomas, 1996). Lectins on cell surfaces mediate cell–cell interactions by recognizing specific and complementary carbohydrates on adjacent cells (Brandley and Schnaar, 1986). CAMs such as integrin, cadherins and selectins are the transmembrane glycoproteins that mediate cell–cell and cell–ECM adhesions by the recognition of specific receptors on other cells or ECM (Edelman, 1983; Edelman and Crossin, 1991). Several important, fundamental questions remain in our understanding of these events: How do receptor proteins interact with their ligands and initiate specific transduction pathways? How do lectins bind with their specific carbohydrates and mediate relevant cell–cell recognition and cell–ECM adhesion? How do CAMs interact with ECM and make cells grow on different types of surfaces? What happens if these interactions are blocked by exogenous substances?

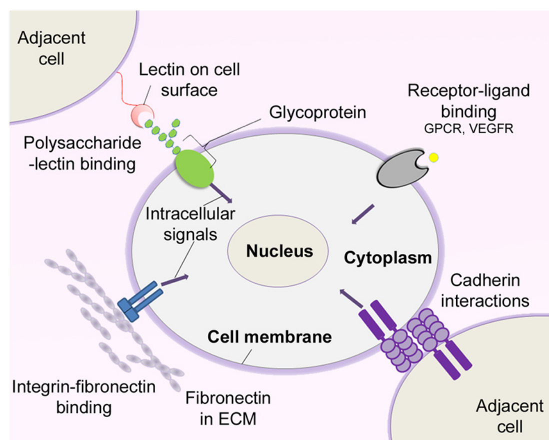


**Fig. 1.** Typical biomolecular interactions that can be measured on the surface of cells.

All these recognition events on cell surfaces are driven by molecular scale interaction forces. The interaction forces of proteins with their ligands contain fundamental biophysical data that can enable us to quantitatively elucidate the relevant cellular signal transduction processes. Interactions on cell surfaces have fundamental roles for characterizing various normal processes including cellular growth, differentiation, junction formation and polarity (Albelda and Buck, 1990; Aplin et al., 1998) or pathological processes in living organisms, such as cellular adhesion, infection and cancer cell metastasis (Gorelik et al., 2001; Ohyama et al., 1999; Sharon and Lis, 1989). In addition, these interaction forces provide a mean for evaluating the selectivity and specificity of various biological probes that can be useful in developing cell-specific bio-analytical and biomedical devices (Jelinek and Kolusheva, 2004; Turner, 2000; Zheng et al., 2005). Consequently, measuring these forces directly has implications in unraveling the molecular basis of relevant biological and pathological processes on cell surfaces, as well as in developing new tools for disease diagnosis and detection, or drug screening at a molecular level (Kim et al., 2007; Yu et al., 2011).

Force spectroscopy as a dynamic analytical technique, allows the measurement of interaction forces at the level of individual molecules, which cannot be obtained from conventional ensemble measurements (Hugel and Seitz, 2001). In this context, “force spectroscopy” is not used in the sense of traditional spectroscopy, which is based on the interaction of radiation with matter (Carvalho and Santos, 2012). Typically, in this process, the pair-wise interaction between (bio)molecules is measured by immobilizing one (bio)molecule on a substrate, while the other attached to another surface or a probe (for example, a magnetic bead or a stiff cantilever). The force is then derived from the deviation of the surface or the probe from its equilibrium position (Israelachvili et al., 2010; Lin et al., 2005; Molloy and Padgett, 2002; Neuman and Nagy, 2008). The technique of force spectroscopy has been used to study the unfolding of single proteins and nucleic acid structures by mechanically stretching the biomolecule across two ends immobilized to surfaces (Hyeon and Thirumalai, 2007; Zhuang and Rief, 2003). To date, several different kinds of force spectroscopy techniques have been employed for determining these forces of interaction. These include optical tweezers, magnetic tweezers and atomic force microscopy (AFM) (Gosse and Croquette, 2002; Krasnoslobodtsev et al., 2007; Leckband et al., 1992; Merkel et al., 1999; Moffitt et al., 2008), all of which operate within specific limits of sensitivity and range of forces. The principles, applications and limitations of these three techniques were recently summarized in an excellent review (Neuman and Nagy, 2008). Among them, AFM has rapidly emerged as a versatile tool widely used over the last couple of decades. The unique advantage of the AFM is the ability not only to image single molecules with nanoscale resolution, but also measure inter- and intra-molecular interaction forces with piconewton

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