NanoTech meets NanoBio: Nano-architectured cell surface mimics for binding of the influenza virus

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Multivalency is the phenomenon that describes the interaction between multivalent receptors and multivalent ligands, and plays a pivotal role in biology, in particular in protein-carbohydrate interactions, for example in the attachment of viruses or bacteria to cell membranes [1-3]. The influenza virus binds to cell walls through multiple sialyl-terminated carbohydrates (SLNs) non-covalently interacting with its hemagglutinin coat proteins. This interaction is weakly multivalent in nature [4], and it is expected to be superselective [5], explaining the large differences between virus affinities by small mutations in their receptor binding domain [6].

A key aspect of the multivalent interaction of viruses at cell membranes is its strong dependence on the receptor density displayed at the surface. We here show the development of various chemistries to control receptor densities at a surface.

Surface gradients of receptor-modified supported lipid bilayers (SLBs) [7] are developed to visualize and quantify the receptor density dependence in one microscopic image. The gradients in biotin-functionalized SLBs are visualized by using fluorescently labeled streptavidin, onto which biotinylated SLNs are attached. The binding of dye-labeled influenza viruses provides a full picture of the multivalent binding of the viruses to the SLB in a single fluorescence image. Such images show a steeply, nonlinear dependence of the virus coverage on the SLN density, which is the hallmark of superselective binding.

The description of the multivalent, density-dependent data by a thermodynamic model allows quantification of the threshold density, comparison of binding selectivities for different virus strains, and a molecular understanding of the supramolecular binding energy landscape. This supramolecular and nanoscopic picture links fundamental molecular aspects of binding to biological processes of antigenic drift and the, so far unpredictable, transfer of viruses from one species to another.

References

[1] M. Mammen, S.-K. Choi, G. M. Whitesides, *Angew. Chem. Int. Ed.* **1998**, *37*, 2754

[2] A. Mulder, J. Huskens, D. N. Reinhoudt, *Org. Biomol. Chem.* **2004**, *2*, 3409

[3] C. Fasting, C. A. Schalley, M. Weber, O. Seitz, S. Hecht, B. Koksch, J. Dernedde, C. Graf, E.-W. Knapp, R. Haag, *Angew. Chem. Int. Ed.* **2012**, *51*, 10472

[4] D. Di Iorio, M. L. Verheijden, E. van der Vries, P. Jonkheijm, J. Huskens, *ACS Nano* **2019**, *13*, 3413

[5] F. Martinez-Veracoechea, D. Frenkel, *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 10963

[6] X. Xiong et al., *Nature* **2013**, *497*, 392

[7] J. van Weerd, S. O. Krabbenborg, J. Eijkel, M. Karperien, J. Huskens, P. Jonkheijm, *J. Am. Chem. Soc.* **2014**, *136*, 100; S. O. Krabbenborg, J. van Weerd, M. Karperien, P. Jonkheijm, J. Huskens, *ChemPhysChem* **2014**, *15*, 3460