Max-Planck-Institut für Struktur und Dynamik der Materie

Max Planck Institute for the Structure and Dynamics of Matter

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CFEL Seminar room III, EG.080 (Bldg. 99)

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"Liquid-Phase Electron Microscopy of Cells and Nanomaterials in Liquid"

Transmission electron microscopy (TEM) has traditionally been associated with the study of thin solid samples in vacuum. With the availability of reliable thin membranes of silicon nitride, TEM of liquid specimens has become accessible with nanoscale resolution in the past decade [1]. The usage of scanning transmission electron microscopy (STEM) presents a novel concept to study membrane proteins within whole mammalian cells in their native liquid environment [2]. The cells in liquid are placed in a microfluidic chamber enclosing the sample in the vacuum of the electron microscope, and are then imaged with STEM. It is not always necessary to enclose the cells in the microfluidic chamber. For many studies, it is sufficient to obtain information from the thin outer regions of the cells, and those can be imaged with high resolution using environmental scanning electron microscopy (ESEM) with STEM detector [3]. A third option is to cover a liquid specimen under a thin membrane of graphene providing the thinnest possible layer [4].

Liquid STEM was used to explore the formation of HER2 homodimers at the single-molecule level in intact SKBR3 breast cancer cells in liquid state [3]. HER2 is a membrane protein and plays an important role in breast cancer aggressiveness and progression. Data analysis based on calculating the pair correlation function from individual HER2 positions revealed remarkable differences its functional state between rare- and bulk cancer cells with relevance for studying the role of cancer cell heterogeneity in drug response. We discovered a small sub-populations of cancer cells with a different response to a prescription drug [5].

Liquid STEM was also used to explore the behavior of nanoparticles in liquid in time-lapse experiments. It was discovered that nanoparticle movement in close proximity of the supporting silicon nitride membrane was three orders of magnitude slower than what was expected on the basis of Brownian motion for a bulk liquid [6], pointing to the existence of a layer of highly ordered liquid at the membrane.

References

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[2] de Jonge, N., et al. *Proc. Natl. Acad. Sci.,* **106**, 2159-2164 (2009)
[3] Peckys, D.B., et al. *Sci. Adv.,* **1**, e1500165 (2015)
[4] Dahmke, I.N., et al. *ACS Nano,* **11**, 11108-11117 (2017)
[5] Peckys, D.B., et al. *Mol. Biol. Cell,* **28**, 3193-3202 (2017)
[6] Verch, A., et al. *Langmuir,* **31**, 6956–6964 (2015)

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