

IMPROVING DRUG DISCOVERY USING QCM-D

Screening of compound interactions with cells and protein drug targets is often essential in drug discovery. Quartz Crystal Microbalance with Dissipation monitoring, QCM-D, enables such measurements in real-time.

In particular, the ability of the QCM-D technique to sense conformational and structural changes in molecular layers or whole cells on the sensor surface using its unique ability to probe changes in softness (energy dissipation) provides a major advantage. These capabilities have potential within drug discovery, enabling both detection of potential new pharmaceutical candidates in drug target screening assays, and improved understanding of target interactions mechanisms.

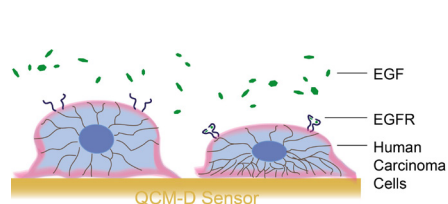


FIGURE 1. Illustration of carcinoma cells on a QCM-D sensor, and the exposure to EGF. Addition of EGF causes changes in the cytoskeleton.

Cellular responses to growth factors in human carcinoma cells [1]

QCM-D provides a sensitive platform for cell-surface interactions which can be monitored in real-time. Here, human carcinoma cells attached to the sensor ex-situ and their interaction with the epidermal growth factor (EGF) was analyzed [1] (Fig. 1). The binding of EGF to the EGF receptor (EGFR) results in cytoskeleton rearrangements in the cells which are successfully probed by QCM-D as changes in the viscoelasticity of the cell layer.

Protein conformational changes caused by small compounds [2][3]

Several publications have highlighted QCM-D as a useful tool in protein drug target screening. These assays depend on conformational changes to the tertiary structure of the proteins upon binding of small compounds. Here, the unfolding of the protein plasminogen was probed upon addition of lysine analogues [2] (Fig. 2). Similarly, conformational re-arrangements have been studied in the HIV-1 envelope protein [3]. The His-tagged recombinant HIV-1 envelope protein was immobilized on the QCM-D sensor and its interactions with different compounds were followed in real-time. In both studies changes in the energy dissipation proved crucial for understanding conformational events.

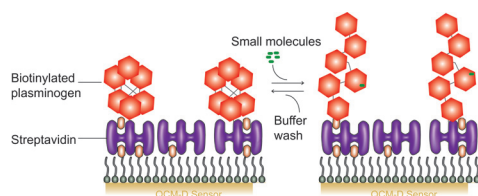


FIGURE 2. Plasminogen protein conformational change due to small molecule interaction.

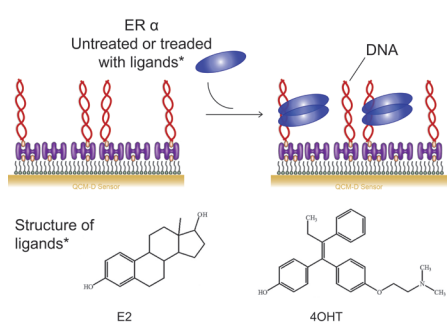


FIGURE 3. Outline of the estrogen-DNA binding assay and structure of the two ligands.

Understanding biomolecular interactions and processes [4][5]

Insights into protein-protein or protein-DNA interactions are of vital importance in drug development. Conformational effects in nuclear receptors, such as the estrogen receptor, is one relevant example [4]. Upon ligand binding the receptors bind to DNA. By immobilization of biotinylated DNA, followed by injection of estrogen receptors in the absence or presence of ligands, the interactions can be studied by QCM-D [4]. Also, processes of self-oligomerization and aggregation of proteins involved in human protein misfolding diseases can be studied using QCM-D. Measurements revealed that oligomers formed by the Alzheimer's disease (AD) associated peptide A β are "softer" than the monomers upon interacting with a model surface [5], something that might be related to their toxicity in AD.

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QCM-D Quartz Crystal Microbalance with Dissipation monitoring

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