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PICOSCOPIC MASS ANALYSIS OF MAMMALIAN CELLS PROGRESSING THROUGH THE CELL CYCLE

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The progression of cells through the cell cycle is a fundamental, physiological process[2]. However, the interplay between the regulation of cell growth and mass and cell cycle awaits accurate physical quantification. Basic questions, such as to what extent the mass of adherent cells is regulated during different phases of the cell cycle, remain to be answered[3]. To date, mass regulation in different states of the adherent cell (for example a cell cycle phase) could not be characterized, since only large population of cells that are not synchronized in their cycle state are commonly probed. To gain fundamental insights in cell mass regulation thus requires the mass characterization of single cells. We have recently developed a method to noninvasively measure the mass of single adherent mammalian cells at high mass and time resolution[1]. This picbalance is based on a photothermally actuated microcantilever, which is mounted onto an inverted microscope and operates under incubator conditions (Fig. 1a). For mass measurements, a single cell is adhered to the microcantilever. The attachment of a cell to the cantilever changes the natural resonance frequency of the cantilever. In order to increase mass sensitivity, a low-power, intensity modulated blue laser is focused on the base of the cantilever to induce small oscillations of 1-15 Å (Fig. 1b). Amplitude, resonance frequency and phase of the cantilever oscillation are optically recorded by an infrared laser. The phase, which is the delay between laser actuation and mechanical response of the cantilever, is 90° at the natural cantilever resonance frequency (Fig. 1c). By determining the natural resonance frequency of the cantilever with and without an attached cell, the mass of a cell is measured (Fig. 1d).

In this proposal, we will address how different adherent cells progressing through the cell cycle regulate growth and mass by applying and further developing our recently invented picobalance. Using the picoscopic device, in combination with time-lapse fluorescence microscopy, fluorescence cell state trackers, and biological and chemical perturbations will enable us to monitor and correlate cellular growth and mass with cell cycle phase and morphology.

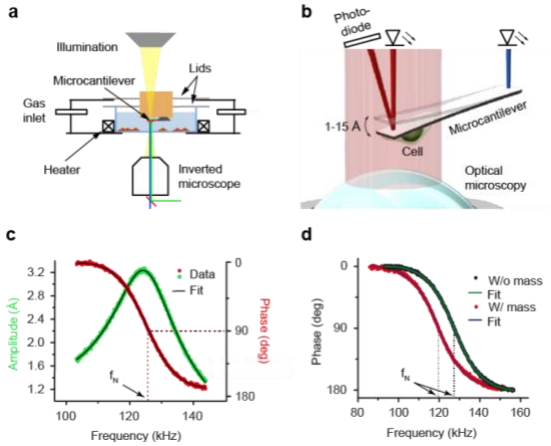

Figure 1. Working principle of the picobalance. **a)** A mammalian cell is attached to a microcantilever and is placed in an environmental chamber, which regulates temperature, gas atmosphere and humidity to ensure cell culture conditions. **b)** To measure the mass of the cell, the cantilever is actuated by an intensity modulated blue laser at its natural resonance frequency (f_N). The movement of the cantilever is monitored by a second infrared laser. The cell can be microscopically observed at all times of the experiment. **c)** A typical cantilever amplitude (green) and phase (red) response of a micro-cantilever measured in cell culture medium is shown. The fit (thin black lines) re-presents a driven and damped harmonic oscillator model. **d)** Phase curves of a cantilever with (red) and without (black) a reference weight is shown. The shift of the resonance frequency is used to calculate the cell mass. Thin lines are fits.

References

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