

TSF17-2017-000232

Abstract for an Invited Paper
for the TSF17 Meeting of
the American Physical Society

Tracking Reactive Oxygen Species Activated Drug Activity on DNA Chips

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Anticancer treatments that induce cancer-selective DNA damage represent a promising strategy for therapy. The drugs RAC1 and RAP are activated by elevated levels of hydrogen peroxide in certain cancer cells and presumably function by forming phenol adducts on DNA bases. It is hypothesized that these adducts interfere with hydrogen bonding, thus lowering the stability of DNA, showing a potential link to anticancer activity. Using electrochemical chips to establish changes in duplex stability, this correlation is observed. Chip signals are highly sensitive to structural alteration of DNA and enable study of real-time activity of DNA damaging drugs that disrupt DNA double helix stability, such as RAC1 and RAP. Duplex stability changes in response to drug treatment were tracked by room temperature current-voltage characteristics on DNA chips under biologically relevant conditions, particularly with square wave voltammetry peak heights. Concentration dependence of both drugs and the hydrogen peroxide that activates the drugs were determined as well as the optimum pH and the kinetics of drug-adduct formation were followed. This work supports the notion of DNA destabilization by reactive oxygen species-activated drugs and clarifies the timescales of activity.