

5th World Congress on Cancer Therapy

September 28-30, 2015 Atlanta, USA

Cancer cell- state plasticity and resistance to therapy

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Therapeutic resistance has been proven to be one of the foremost obstacles limiting the clinical efficacy of cancer drug treatments including targeted therapies for non-small cell lung cancers (NSCLC) harboring activating EGFR mutations. Recent evidence indicated that the intrinsic heterogeneity of tumors is one of the main mechanisms of acquired drug resistance. Here we show that NSCLC harboring EGFR mutations can become resistant to inhibition of EGFR via a novel epigenetic mechanism. By modeling erlotinib resistance, we identified a drug-tolerant cell population that is already present in NSCLC populations prior to drug treatment. These erlotinib-resistant cells are regulated epigenetically and represent an alternative cell state in which cancer cells can reside in. The transition between these different cell states modifies the cell signaling network, reworks cancer cell dependency and induces a hypermutable phenotype. These findings provide a rationale for incorporating novel first-line combination therapies in the treatment of NSCLC harboring EGFR-activating mutations.

Biography

Raffaella Sordella after completing her PhD studies at Turin Univeersity did her postdoctoral training at Massachusetts general hospital and Harvard medical school. Currently she is an associate Professor at Cold Spring Harbor Laboratory.

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