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Rapid evolution of drug resistance of multiple myeloma in the microenvironment with drug gradients AMY WU, Princeton University, QIUCEN ZHANG, University of Illinois at Urbana-Champaign, GUILLAUME LAMBERT, University of Chicago, ZAYAR KHIN, ARIOSTO SILVA, ROBERT GATENBY, Moffitt Cancer Center, JOHN KIM, NADER POURMAND, University of California at Santa Cruz, ROBERT AUSTIN, JAMES STURM, Princeton University — Drug resistance in cancer is usually caused by the spatial drug gradients in tumor environment. Here, we culture multiple myeloma in a gradient from 0 to 20 nM of doxorubicin (genotoxic drug) across 2 mm wide region for 12 days. The myeloma cells grew rapidly and formed 3D colonies in the regions with less drug concentration. However, we have seen emergent colonies forming in regions with drug concentration above the minimal inhibitory concentration in less than one week. Once the cells have occupied the regions with less drug concentration, they tend to migrate toward the regions with higher drug concentration in a collective behavior. To characterize their resistance, we collect them from this microfluidic system, for further analysis of the dose response. We find that the IC50 (drug concentration that inhibits 50% of controlled population) of the cells, undergone a drug gradient, increase 16-fold of the wildtype cells. We further discover that these resistant cells express more Multidrug Resistance (mdr) protein, which pumps out the drugs and causes drug resistance, than the wildtype. Our current works on RNA-sequencing analysis may discover other biomolecular mechanisms that may confer the drug resistance.

Amy Wu
Princeton University

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