Abstract Submitted
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Emergence of therapy resistance in multiple myeloma in heterogeneous microenvironment[1] AMY WU, Princeton University, QIUCEN ZHANG, University of Illinois Urbana-Champaign, GUILLAUME LAMBERT, University of Chicago, ZAYAR KHIN, ARIOSTO SILVA, ROBERT GATENBY, Moffitt Cancer Center, HYUNGSUNG KIM, NADER POURMAND, University of California Santa Cruz, ROBERT AUSTIN, JAMES STURM, Princeton University — Cancer chemotherapy resistance is always a problem that is not clear considering spatial heterogeneity in the tumor microenvironment. We culture multiple myeloma in a gradient from 0 to 20 nM of doxorubicin (genotoxic drug) across 2 mm wide region in a microfluidic device which mimics the tumor microenvironment with a chemotherapy drug gradient and microhabitats. Resistance of the multiple myeloma cells to doxorubicin emerged within two weeks. For the resistant cells evolved from the devices, the doxorubicin concentration that inhibits 50% of the controlled population increased by 16-fold than the parental cells. Whole transcriptome sequencing revealed that 39% of newly acquired mutational hotspots (the genes with more than 3 non-synonymous point mutation) of the resistant cells are involved in apoptosis and DNA repair. On the other hand, 40% of the non-mutated genes that are abnormally regulated in the resistant cells, are involved in metabolism, biosynthesis, and biomolecular transport. Among them, metabolic drug efflux pumps and oxidative stress scavengers are up-regulated to reduce the cytotoxicity of doxorubicin and further result in the resistance. The roles of the spatial drug gradients and microhabitats in rapid emergence of cancer resistance will be discussed.

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