CHEMICAL ENGINEERING
UNIVERSITY of WASHINGTON

SEMINAR

Alişya Anlaş
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Matrix stiffness suppresses growth, induces chromosome mis-segregation and increases genomic variation in cancer spheroids

Monday August 28th
Lecture 4:00-5:00 p.m. | Physics/Astronomy Auditorium (PAA) A110
Reception 5:00-6:00 p.m. | Benson Hall Lobby

Bio

Bio Alişya Anlaş is a postdoctoral researcher with Prof. Dennis Discher at the University of Pennsylvania. As a chemical and biological engineer, she uses engineered tissue culture models to uncover how the mechanical properties of the tissue microenvironment regulate hallmarks of cancer such as sustained proliferation, survival, genomic instability, and immune evasion. Her doctoral studies with Celeste Nelson revealed that autophagy is a mechanically-regulated cell survival mechanism that contributes to chemoresistance in breast cancer. Her postdoctoral work investigates how microenvironmental stiffness regulates cell division errors including chromosome missegregation. As a pilot grant awardee at Penn's NSF Center for Engineering Mechanobiology, she also studies the impact of confined migration on macrophage-based immunotherapies. Alişya is committed to increasing public engagement with science, enhancing inclusivity, and expanding access to STEM education. She has taught college algebra with the Prison Teaching Initiative (PTI) at Princeton and has coordinated several community outreach events with Princeton Citizen Scientists, YWCA's Breast Cancer Resource Center, and PTI including "The Prison and the Academy", "The Day of Action", and the workshop series, "Science and Intersectionality".

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Abstract

Matrix stiffness suppresses growth, induces chromosome mis-segregation and increases genomic variation in cancer spheroids

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Genomic instability, the inability of a cell to pass on its genetic information accurately, is a hallmark of cancer. During cancer progression, the extracellular matrix stiffens to mechanically confine cancer cells, however it is not known whether such changes in the microenvironment contribute to chromosome loss. Here, we employed engineered tissue culture systems and cancer cell lines carrying chromosome reporters generated using the CRISPR/Cas9 system to investigate whether matrix stiffness regulates chromosome loss (**Figure 1A**). We cultured lung cancer spheroids in viscous methylcellulose or in agarose hydrogels of varying elastic moduli (**Figure 1B-C, Figure 2A**), then assessed cell division and chromosome loss. Our findings indicate that stiff microenvironments suppress cell division (**Figure 2B**) but enhance chromosomal aberrations such as micronuclei (**Figure 2C-D**) and chromosome loss (**Figure 2E-F**). We also show that stiff microenvironments induce genomic variation and increase tumor heterogeneity, which are known to reduce sensitivity to cancer therapeutics. In addition, our data suggest that cancer cells exhibiting chromosome loss are viable and can pass on these chromosomal aberrations to future generations (**Figure 2G**). Overall, our findings highlight that the mechanical properties of the tumor microenvironment regulate genomic instability -a major limiting factor in the treatment of solid tumors. Uncovering and targeting pathways that lead to chromosomal instability could help reduce resistance to therapy and improve patient outcomes.

Figure 1. A. GFP is fused to one allele of the constitutively active Lamin B1 ge ne on chromosome 5 of H23 lung cancer cells. Cell divisions that result in chromosome loss can be traced by tracking GFP loss. **B.** A population of lung cancer cells carrying the chromosome reporter are cultured in methylcellulose or agarose hydrogels with **C.** varying elastic moduli resprese ntative of healthy lungs or a lung tumor.

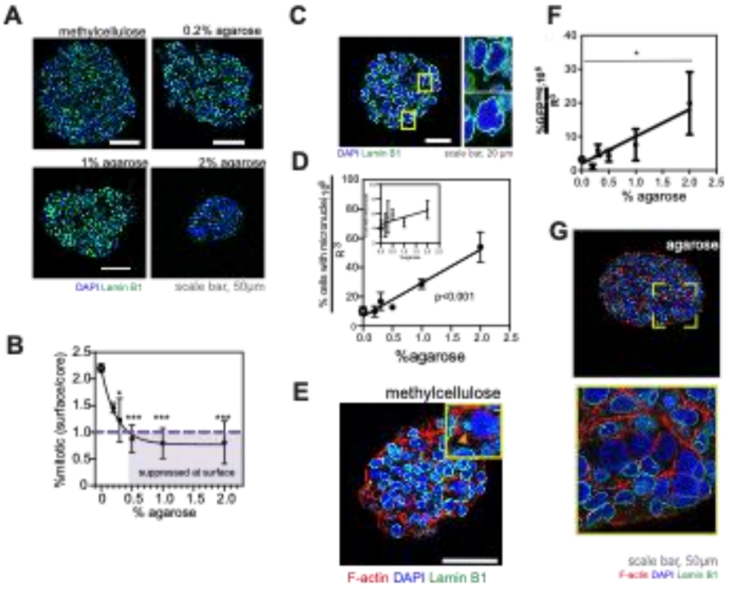

Figure 1. A. H23 lung cancer spheroids are cultured in viscous methylcellulose or agarose hydrogels (0.2-2%). Increased stiffness reduces the size of spheroids. **B.** The percentage of mitotic cells is reduced for spheroids cultured in agarose hydrogels. **C.**Micronucleus formation is evident in H23 spheroids. **D.** The number of micronuclei increase in spheroids cultured in stiff hydrogels. **E.** Chromosome loss is characterized by analyzing GFP-negative nuclei (yellow box). These nuclei are occasionally found next to GFP-positive micronuclei. **F.** The percentage of GFP-negative cells, i.e. percentage of cells that have lost a chromosome, increases in spheroids cultured on stiff hydrogels. **G.** Cells with chromosome loss (yello box) are viable and can continue to divide, as evident by GFP-negative colonies.