George Lab
Transport and Tissue Remodeling

Undergraduate Student Guidelines and Rules

Goal. Undergraduate students can make significant contributions to the overall research mission of the lab. However, the primary goal is to simply provide a rewarding introductory experience to basic and applied research in an academic setting. This experience should include learning current experimental techniques in the broad field of tissue engineering, basic experimental design, data analysis and interpretation, and scientific writing.

Time Commitment. It is understood that your primary objective is to complete your undergraduate coursework; thus, the time commitment is expected to be 9-12 hours/week during the academic year, and 40 hours/week in the summer.

Primary Mentor. Every undergraduate will be assigned a primary mentor. The primary mentor will either be a doctoral student or postdoctoral researcher, and will be responsible for the overall training of the undergraduate researcher. The primary mentor should approve the planning, execution, and interpretation of all experiments. The undergraduate researcher and mentor should plan to meet with Dr. George no less than once per quarter.

Independent Study (Academic Credit). Each undergraduate researcher is expected to work in the lab the first semester to learn basic techniques in cell culture and to develop a plan for independent study. There is no compensation or academic credit for the first quarter. Following the first quarter, undergraduate researchers in the George lab are eligible to receive academic credit for their work. To register for academic credit, students must fill out the Biomedical Engineering Undergraduate Research Form (http://bme.ucdavis.edu/undergrad/files/2010/10/199-LAB-Credit-Petition.pdf) and return the form to Rosalind Christian in the BME office by the 10-day drop deadline. Each credit unit is equal to 3 hours/week, and undergraduate researchers are expected to register for 3 (9 hours/week) or 4 (12 hours/week) credit units. At the end of each quarter, students are expected to write an abstract about their work in the lab, as if they were preparing to attend a scientific conference (see example below). Grading is on a P/NP basis.

Summer Research Fellowship and Work Study. There are limited opportunities to work in the lab and receive financial compensation. All undergraduates are strongly encouraged to work in the summer during which significant progress and momentum on the research project can be made. The primary option for funding is summer research fellowships available from UC Davis the School of Engineering. These fellowships generally provide a summer stipend. If the application for a fellowship is not successful, and funds are available, the student can receive ca comparable stipend.

Example Abstract

The effect of chemokine gradients on directional collective migration of breast tumor cells

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Introduction Tumor cell migration is a fundamental step in tumor progression and a driving force behind metastasis. Conventional thought purports that metastasis occurs through individual cell migration to target organs. However, recent studies of tumor migration patterns demonstrate that the majority of solid tumors migrate as a multicellular unit (collective migration). These observations have also demonstrated that collective migration may alter cell-signaling patterns, resulting in differential tumor response to therapies. Much work has been done to investigate how tumor microenvironmental features (e.g., hypoxia) impact individual cell migration whereas it is still relatively unknown how these features can alter collective migration. Thus, there is much interest to determine what microenvironment features initiate and signal to a collective tumor unit to initiate and guide migration. Prior studies in our lab has demonstrated that CXCR4 and discoidin-domain receptor 2 (DDR2; collagen receptor and mechanosensor) are two proteins that are responsive to changes in chemokine gradients. Furthermore, transcriptome profiling and histologic analysis of primary human invasive breast cancer tissue compared to normal breast tissue reveals higher expression of both CXCR4 and DDR2 that are associated with poor outcomes. Therefore, the objective of this study was to investigate how biochemical changes in the tumor microenvironment can impact differential collective migration response of breast tumor cells via CXCR4 and DDR2 signaling.

Materials and Methods We designed and constructed a microfluidic "cancer-on-a-chip" device to mimic tumor microenvironment features of a chemokine gradient and interstitial fluid flow. We used primary mouse tumor cells isolated from mammary tumor virus-polyoma middle T antigen (MMTV-PyMT) mice as our model cells because MMTV-PyMT transgenic mice develop spontaneous primary tumors in the mammary glands, over 90% of these mice go on to develop lung metastases, and prior studies demonstrate these tumor cells migrate in a collective manner. After isolating organoids from MMTV-PyMT mice, we loaded spheroids of tumor cells into our devices, and cultured them in hypoxia (1% O_2) for 48 hours. After culturing in hypoxia, we established a SDF1 chemokine gradient (ligand receptor to CXCR4) and performed live-cell imaging over 18 hours to quantify changes in collective migration. Using Metamorph, FIJI, and custom-designed Matlab code, we quantified migration direction, efficiency, and velocity. We also performed second harmonic (SHG) imaging to quantify changes in collagen alignment, and immunostaining for CXCR4 and E-cadherin (cell-cell adhesions). Additionally, we used a CXCR4 inhibitor (AMD3100) and DDR2 knockout system to investigate whether or not these two proteins are essential for sensing tumor microenvironment and subsequent collective migration.

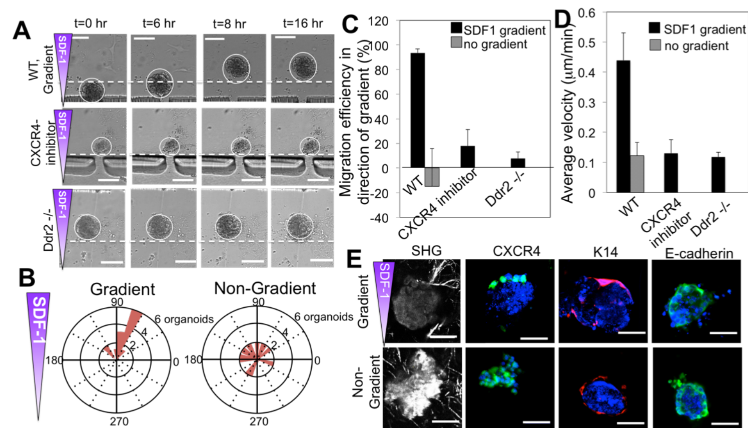

Figure 1: Primary mouse organoids migrate collectively in the direction of an SDF1 chemokine gradient in vitro (A) Live-cell imaging (scale bar = 100 µm) (B) Migration direction (C) Migration efficiency in direction of gradient (D) Average velocity. (E) SHG imaging (collagen) and staining of CXCR4 (green), K14 (red), and E-cadherin (green) (DAPI counterstain, scale bar = 25 µm).

Results and Discussion Findings reveal collective migration occurs in the direction of the SDF1 gradient, and is dependent on both CXCR4 and DDR2. When tumor cells migrate in the direction of the chemokine gradient, significantly higher velocities (0.4 µm/min) are observed compared to no gradient conditions. Furthermore, SHG imaging indicates matrix alignment in the direction of migration, and CXCR4 and K14 (the putative marker of a leader cell) were localized to cells at the leading edge of the migrating organoid.

Conclusions Together, our findings suggest that both CXCR4 and DDR2 have essential roles in guiding collective migration through sensing of the SDF1gradient and collagen matrix in the tumor microenvironment. Furthermore, studies indicate uneven localization of CXCR4 and K14 may contribute to the direction of migration.