Chromosomal Regulation

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Chromosomes are paradoxical molecules. On the one hand, they provide stability, enabling faithful propagation of the DNA sequence. On the other hand, they provide flexibility in how this DNA sequence is used, enabling the emergence and memorization of alternative states during cell differentiation. Our group researches how the constellation of non-coding regulatory elements scattered across chromosomes, such as enhancers, patterns the transcription of protein-coding genes. We are especially interested in deciphering the molecular mechanisms driving 3D chromatin folding and understanding the roles they play as pluripotent stem cells differentiate. (More details are on https://noralab.ucsf.edu.)

While the impact of the COVID-19 epidemic on our work is obviously a source of great frustration, I find inspiration in my colleagues who use it as an opportunity to reevaluate some of our default research habits. We have to come up with creative ways to better share reagents and resources within and between groups, for example by incorporating video demonstrations in our protocols and training procedures. I noticed changes in peer review, with some journal editors engaging more actively in evaluating the feasibility and legitimacy of requested revisions. Online seminars, conferences, and communities are emerging as creative new ways to connect. Sharing lab space with two other new chromatin groups, led by Abigail Buchwalter and Daniele Canzio, is immensely helpful to myself and my trainees during these times.

Greater than the Sum of Its Parts

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Adult stem and progenitor cells (SCs) maintain our tissues in health and disease. My group studies the impact of inflammation on skin and intestinal epithelial SCs and the enduring memory that forms thereafter. Just as SCs learn from adversity, so too have my experiences with the ongoing pandemic been educational. 1 year and 9 months after starting my lab, I found myself in an epicenter of the COVID-19 pandemic. The city that never sleeps shut down. Our studies had only started taking off and exciting results were beginning to emerge when research operations came to a screeching halt. Animal colonies were contracted, cell lines were frozen, equipment was unplugged, and, most disheartening of all, students and postdocs were stranded.

At first, I responded by trying to be as efficient as possible. I encouraged trainees to write fellowships, learn to code, and compile manuscripts. Exhausted by quarantine and a self-imposed sense of urgency, I quickly realized that productivity was a misplaced priority. Our data-heavy lab meetings morphed into ad hoc discussions of personal struggles, interesting papers, and cool experimental avenues to explore in the future. I learned that people are what make the science fun and worth doing. While the last 5 months have been barren of data, I am energized by the lab’s stimulating discussions. Despite the physical separation, seven remarkable individuals have come together as a team and I see my lab becoming greater than the sum of its parts.

LSCs: Seek and Destroy

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Molecular and cytotoxic therapies in leukemia can often induce remission without achieving complete disease eradication, potentially resulting in relapse. A better understanding of cell-to-cell heterogeneity is crucial for the rational design of therapeutic strategies accounting for myeloid leukemia complexity. One aspect of this heterogeneity is its hierarchical structure, with leukemic stem cells (LSCs) being the only cells capable of sustaining and propagating the tumor. My group’s research revolves around understanding the biological mechanisms that make LSCs unresponsive to conventional therapies and identifying novel therapeutic targets allowing for their selective immunotherapeutic targeting. By combining single-cell genomics and proteomics with stem cell functional assays, we aim to develop novel strategies to prevent and treat leukemia progression. The COVID-19 pandemic had a tremendous impact on many aspects of our lives, including our research dynamics. Beyond inevitable experimental delays due to labs closure, my biggest concern as a new PI was the weakening of group cohesion and collaborative networks, vital to a young lab. I am proud that everyone in the lab impressively and quickly adjusted to these unprecedented times by shifting their focus to data analysis and creatively finding alternative ways to progress with their projects. A bumpy start in our group’s journey may have turned us into more experienced drivers, well equipped to achieve our next goals.
In 2019, I started my lab to study the interplay between stem cells, metabolism, and cancer. As a junior PI, I am lucky to have a highly motivated international team sharing my enthusiasm for this topic. We study the intestine, a fascinating organ of fast cell renewal supported by dividing stem cells and their well-defined differentiated progeny. Former and ongoing research in my lab showed that metabolic changes in stem cells can trigger and determine epithelial differentiation trajectories. This exciting concept points to factors such as diet, gut microbiota, and even derailed cancer metabolism as potential remodelers of tissue composition. Hence, we investigate both homeostatic and tumorigenic tissue, aiming to contribute to the improvement of conventional therapies. We use a broad range of tools, e.g. live imaging of organoids engineered with fluorescent-based reporters, to dissect the crosstalk between metabolism and stem cell behavior at the single-cell level and with high temporal resolution.

COVID-19 took us by surprise; we went quickly from social distancing protocols to a complete lockdown and cessation of lab work. Despite the growing feeling of uncertainty, we continued our research from home. Our regular online meetings were key to keeping our science going and also served for social support. From this situation we have learned to embrace the unexpected by making the best out of it. Importantly, we learned that difficult times do not appease our passion for science.

The functionality of each organ in our bodies is determined by the structure and correct organization of each tissue component. Tissue architecture is ensured by a perfect equilibrium between each individual cell, its neighbors, and the physical environment. In particular, this is tightly regulated in epithelia that are naturally subjected to different mechanical perturbations and constantly renewed through our lives thanks to stem cells and progenitors able to regenerate entire tissues. My research focuses on understanding how mechanical forces shape tissue architecture and change epithelial stem cell dynamics during homeostasis and organ growth. After 8 years of postdoctoral training first at the University of Padova in Italy and then at the Université Libre de Bruxelles in Belgium, I was thrilled to move to Denmark to establish my laboratory at DanStem, University of Copenhagen. But while I was starting to plan the new beginning, the world was shocked by the pandemic crisis and my relocation was postponed. I was very glad about the support I received during the shutdown from my previous and current institutions, and I was impressed by the courage with which all my colleagues have faced the situation, cooperating to efficiently solve countless organizational problems. Now, I am finally ready to start, with the renewed belief that establishing a collaborative and friendly environment is a fundamental step to shape a productive team capable of facing future challenges.

Do leukemic cells have a particular niche, and if so, how do they interact with it? That was the question I chased during my wonderful time in Cristina Lo Celso’s lab in London. It still is the question I am asking today. In 2018, I relocated back to Portugal to resume my clinical training, initiate a faculty position at the University of Porto, and start my research program at i3S. After securing funding, our team established key experimental tools to explore niche-leukemia interactions and to add a new element, iron. I was fortunate to have the unique mentorship of the iron expert Graça Porto and fantastic core facilities that helped us kickstart our work. To be literally between the bench and the bedside was and is a challenge. But the brilliant group of researchers that embarked on this journey with me and a newly arrived baby made my work as a PI a bit like a functional hematopoietic stem cell after 5-FU treatment: productive but in place—only possible with the proper microenvironment. COVID-19 was an unexpected insult. It made us stop our beloved wet lab work, downsize mouse colonies, and interrupt rederivations. We lost funding time. But it also gave us the opportunity to analyze and re-interpret data. And more importantly, it gave us a place to “walk the idea.” We looked at our questions from new angles and it gave us new perspectives. The return has been slow but newly guided. We hope the latest experiments will help us turn the ideas into concepts.