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Focus Session: Physics of cancer

Programme:

- Claire Wyman (Erasmus MC) – A tumor suppressor at work, spying on Brca2 in live cells
- Peter Friedl (RU & University of Texas) - Biophysics of cancer invasion: mechanisms, limits and implications
- Jacco van Rheenen (Hubrecht Instituut & UMCU) - Subcellular and real-time imaging of metastasis in living mice
- John van Noort (UL) - Physics of the genome: chromatin organization

Session leader: Thomas Schmidt (UL)

Abstracts:

Claire Wyman (Erasmus MC) - A tumor suppressor at work, spying on Brca2 in live cells

Cancer results from changes in previously normal cells allowing them to divide without control and invade other tissues. The multiple molecular changes that promote and cause cancer can be understood in the framework of a set of acquired cellular characteristics. This framework, worked out in the past decades, depicts cancer as a deterministic process. It is clear that cancer progression is not strictly deterministic, but is influenced by complex interactions networks within cells and between cells and tissues.

Genome maintenance processes, essential for avoiding cancer, involve the coordinated action of many proteins repairing DNA damage and initiating cellular responses to avoid genome instability. Maintaining genome integrity by homologous recombination involves coordinating the action of many proteins within the cell nucleus. To understand how proteins function in such complex interaction networks details of their *in vivo* behavior need to be defined and quantified. For this purpose we are analysing the mobility of Brca2, an essential homologous recombination protein, in live cells. We observed that nuclear Brca2 exists in oligomeric clusters, has heterogeneous mobility and that DNA damage increased binding to immobile nuclear locations. Rad51-GFP displayed mobility similar to Brca2, indicating interaction between these proteins observed in real-time at the single-particle level that was disrupted by expression of the BRC Rad51 interaction domain of Brca2. These studies advance our understanding of how nuclear proteins are coordinated in time and space to achieve on-demand functions like DNA repair.

Peter Friedl (RU & University of Texas)- Biophysics of cancer invasion: mechanisms, limits and implications

Different modes of cancer cell invasion contribute to local tissue invasion and initiation of metastasis, however the underlying mechanisms of each migration program, their limits and their relevance to metastasis remain unclear. In models for melanoma, sarcoma and breast cancer, within the same cancer lesion in vivo both single-cell and collective invasion mediate cell dissemination. Using intravital multiphoton microscopy, we here show the how tissue microniches impose diverse cancer invasion modes, either as barrier precluding migration, or as invasion-promoting tracks that enable either collective, single-cell or combined invasion modes. As main routes, non-destructive contact-guidance along preformed multi-interface perimuscular, vascular and –neural tracks of 1D, 2D and 3D topography were identified. Using in vitro analysis of engineered low- and high-density environments, the underlying physical and molecular limits of cancer cell invasion, showing nuclear deformability and ECM space as rate-limiting determinants and modulation by MMPs and mechanotransduction. Using in vivo targeting of beta1/beta3 integrins, unexpected plasticity of invasion, including de novo development of amoeboid dissemination, was associated with enhanced micrometastasis, implicating integrin-independent dissemination as major route to metastasis. In conclusion, cancer invasion and metastasis result from adaptive physicochemical programs that balance cell-intrinsic adhesion and mechanocoupling with encountered physical and molecular cues.

Jacco van Rheenen (Hubrecht Instituut & UMCU) - Subcellular and real-time imaging of metastasis in living mice

Complications due to metastasis, the process where cells detach from a primary tumor to form new tumors at distant sites, are the primary reason why people die from cancer. Although histological techniques have provided important information on metastasis, they only give a static image of tumor cells and their microenvironment and thus compromise interpretation of this dynamic process. To study this dynamic process, we visualize the behavior of single metastasizing cells at subcellular resolution with two-photon intravital imaging (IVM). We have recently developed a Mammary Imaging Window (MIW) to image primary mammary tumors over multiple days. By combing the MIW with fluorescent lineage tracing tools, we intravitally lineage traced mammary tumors growth. Our intravital lineage tracing experiments showed the existence of a small population of cells, referred to as cancer stem cells (CSCs), that maintains and provides growth. Moreover, our experiments illustrated existing CSCs disappear and new CSCs form during mammary tumor growth, illustrating the dynamic nature of these cells.

In order to study how tumor cells arrive, survive and grow at secondary sites, we developed a new imaging window to image abdominal organs such as the liver, which is one of the primary organs for metastasis formation. Using this abdominal imaging window, we are able to visualize how individual tumor cells that arrive at the liver grow into metastases. We observe that single extravasated tumor cells proliferate and form 'pre-micrometastases' in which cells are migratory and lack contact to neighboring tumor cells. Subsequently, the clones condense into micrometastases in which cell migration is strongly diminished, but proliferation continues. By suppressing tumor cell migration in pre-micrometastases genetically or by drugs we reduce the number of metastases, and therefore we conclude that the migration of cells within pre-micrometastases is a novel contributing step in the formation of liver metastasis.

John van Noort (UL) – Physics of the genome: chromatin organization

In eukaryotic cells, DNA is organized in a condensed structure called chromatin. Any processes that involve DNA, including DNA repair, transcription and replication, need prior chromatin processing to make DNA accessible; aberrant processing of chromatin has been implicated in diseases like cancer and neurological disorders. To understand these DNA transactions at a fundamental level it is therefore required to know the structure of chromatin at the molecular scale.

Here I will discuss recent single-molecule experiments that reveal how is DNA folded in chromatin. Single pair Forster Resonance Energy Transfer shows that DNA can spontaneously unwrap from nucleosomes, the basic unit of chromatin. Force spectroscopy reveals a helical folding of chromatin fibers. Using a statistical physics frame work we derive a quantitative description of the mechanics of small chromatin fragments, which can be the basis for a fundamental understanding of the molecular processes involved in cancer.