Seminar/Talk

Cell migration mechanics during tumor cell dissemination and metastasis

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Host: Michael Sixt

Ultra-high resolution multiphoton microscopy of live animals in real time led to the discovery of cause and effect relationships between cells leading to metastasis, relationships otherwise not possible to identify using in vitro models. This has revolutionized our understanding of cancer metastasis. Multiphoton imaging at subcellular resolution in vivo demonstrates that tumor cells form migratory streams with macrophages and move with high persistence to blood vessels under the control of HGF gradients (1). Once at the blood vessel, a cell complex involving the direct contact between a Mena-Hi tumor cell, endothelial cell and macrophage forms the Tumor MicroEnvironment of Metastasis (TMEM). The TMEM structure itself, as well as the gene expression pattern of tumor cells interacting with TMEM, have been validated as prognostic markers for predicting metastasis in breast cancer patients (2, 3). These were the first markers of metastasis in clinical use derived from multiphoton intravital imaging.Intravital imaging has defined the mechanisms associated with the function of TMEM: a) Streaming tumor cells approaching TMEM in vivo use collagen fibers with diameters less than 3 um where cells move the fastest with highest persistence on the narrowest fibers (700 nm 2.5 m); b) These increased migration speeds and persistence are associated with the alignment of actomyosin fibers and focal adhesions along the collagen fibers axial dimension thereby increasing axial force production and suppressing turning frequency; c) As the high speed stream approaches TMEM it results in tumor cell crowding around TMEM causing MenaINV expression in cancer cells in response to macrophage-induced NOTCH signaling (4); d) MenaINV expression supports invadopodium assembly and insertion between endothelial cells leading to transendothelial migration at TMEM (5); e) TMEM is the only site in breast tumors where tumor cell transendothelial migration and intravasation occur (6); f) TMEM are stable structures found at both primary and metastatic tumor sites in breast cancer patients (7). Using the above information we have designed treatment strategies for inhibiting TMEM function and metastasis (8, 9). These treatment strategies are now in clinical trials in breast cancer patients at sites in North American (clinical trials study number NCT02824575).

Wednesday, February 21, 2018 11:00am - 12:00pm
Mondi Seminar Room 2, Central Building

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