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based on *Evidence*

SPECIAL SESSION

Research Session

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RESEARCH SESSION

SYMPOSIUM: BIOPHYSICAL TECHNIQUES FOR MOLECULAR MECHANISM & BASIC RESEARCH FOR CANCER METABOLISM

Spatio-temporal Analysis of Integrin Tension during Cancer Metastasis

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Cancer metastasis is the process that primary cancer cells spread and migrate to other parts of our body. Physical interaction between integrins expressed on cells and their extracellular matrix (ECM) has a considerable impact on the cancer metastasis. However, mechanical dynamics of integrin tension during cell adhesion, spreading, and migration have not been answered clearly. Here, we report how force applied on a single integrin-ligand bond in human non-metastatic and metastatic breast cancer cells influences cell behaviors using a noble single molecule tension sensor, termed tension gauge tether (TGT). Spatio-temporal analysis of changes in the integrin tension during cell adhesion, spreading, and migration reveals that the metastatic cancer cells retain lower levels of integrin tension compared to that of the non-metastatic cancer cells, leading to enhanced performance in migration. In addition, we identify how integrin type (a_vb_3 and a_5b_1) and their integrin tension facilitate formation of 'invadopodia' as well as migration in confined microstructures. Taken together, our results unveil the biophysical role of integrins in the process of metastasis from initial adhesion to migration.

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Metabolic Reprogramming in Cancer Progression

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Mitochondria as a hub subcellular organelle in regulating metabolism and apoptosis play a central and multifunctional role in tumorigenesis and tumor progression. Altered metabolism allow cancer cells to support their deregulated rapid proliferation. Furthermore, mitochondria in cancer enables the rapid adjustment and survival to harsh environmental conditions encountered during the dissemination process including tumor-growing, metastasis-initiating, and dormant cells. Thus, targeting mitochondria has emerged as a promising strategy to reduce risk of recurrence and metastasis. Here, we show that chaperones compartmentalized in mitochondria are required to regulating tumor bioenergetics, adaptation to cellular stress and cell survival. Interference with this process activates a signaling network that involves phosphorylation of nutrient-sensing AMP-activated kinase (AMPK), inhibition of rapamycin-sensitive mTOR complex 1 (mTORC1), and induction of autophagy. Furthermore, using a bioinformatic analysis, we found mitochondrial fission factor DRP1 and MFF were highly upregulated in castration-resistant and neuroendocrine prostate cancer and increased expression of these proteins were correlated with prostate cancer relapse and abbreviated patient survival. Furthermore, we demonstrate that mitochondria fission is critical for metabolic reprogramming, antagonizing apoptosis and autophagy, dampens oxidative stress, and maintains tumor cell proliferation in the face of severe environmental stress. Taken together, this study will accelerate research to understand metabolism of tumors and can provide improved cancer therapy.

Keywords; Mitochondria, Cancer cell death, Cancer metabolism,

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Hypoxia, Cancer Stem Cells and ID2

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Mechanisms that maintain cancer stem cells (CSCs) are crucial to tumor progression. The ID2 protein supports cancer hallmarks including the cancer stem cell state. HIFα transcription factors, most notably HIF2α (also known as EPAS1), are expressed in and required for maintenance of CSCs. However, the pathways that are engaged by ID2 or drive HIF2α accumulation in CSCs have remained unclear. Here we report that DYRK1 kinases (DYRK1A and DYRK1B) phosphorylate ID2 on threonine 27 (Thr27). Hypoxia downregulates this phosphorylation via inactivation of DYRK1 kinases. Activation of DYRK1 kinases requires prolyl hydroxylation by the oxygen-sensing prolyl hydroxylase PHD1 (also known as EGLN2), and the activity of these kinases is stimulated in normoxia. Prolyl hydroxylation of DYRK1 initiates a cascade of events leading to the release of molecular constraints on von Hippel-Lindau (VHL) ubiquitin ligase tumor suppressor function. ID2 binds to the VHL ubiquitin ligase complex, displaces VHL-associated Cullin 2, and impairs HIF2α ubiquitylation and degradation. Phosphorylation of Thr27 of ID2 by DYRK1 blocks ID2-VHL interaction and preserves HIF2α ubiquitylation. In glioblastoma, ID2 positively modulates HIF2α activity. Conversely, elevated expression of DYRK1 phosphorylates Thr27 of ID2, leading to HIF2α destabilization, loss of glioma stemness, inhibition of tumor growth, and a more favorable outcome for patients with glioblastoma. We will also provide new insights towards the significance of the crucial ID2-VHL interaction and regulation of DYRK1 kinases for CSCs and tumor aggressiveness.

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Single-molecule Imaging for Studying Molecular Mechanism for Cancer

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Understanding molecular mechanism of cancer is important for treatment, diagnosis, and drug development. Mutations of DNA generally develop the incidence of cancer, and the mutations are caused by DNA damage. The mutations from DNA damage are suppressed by diverse types of DNA damage repair mechanisms. So far, numerous studies have been performed for the DNA damage repair mechanisms. However, the in-depth molecular mechanism remains elusive. Here we study nucleotide excision repair (NER) using a novel single-molecule imaging technique. NER is one of DNA repair mechanisms that amend DNA damage such as UV-induced thymine dimers or chemical modifications on bases. The failure of NER causes genetic diseases such as xeroderma pigmentosum and Cockayne syndrome. Human XPC-Rad23B (XPC-RAD23B) is the first protein to ignite NER process by sensing DNA lesions. However, the damage search mechanism of XPC-RAD23B remains poorly understood. Here, we investigated the damage search process of XPC-RAD23B using the single-molecule DNA curtain technique, which is concatenating microfluidics, lipid fluidity, and fluorescence microscopy. We observed the movement of XPC-RAD23B on undamaged DNA and found that XPC-RAD23B diffuses along DNA, indicating that XPC-RAD23B finds DNA damage through one-dimensional diffusion. Moreover, we analyzed the diffusion coefficient of XPC-RAD23B, which dramatically increases as salt concentration rises. This shows that XPC-RAD23B finds DNA damage through the hopping mechanism. We confirm this hopping by performing collision with protein obstacles. XPC-RAD23B bypasses the protein obstacles. This indicates that XPC-RAD23B rapidly searches for DNA lesions by bypassing the protein obstacles via hopping.