Dissection of Cancer Metastasis Signalling Pathway with Systems Biology

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Background

Cancer is the leading cause of death worldwide and causes around 7 million deaths annually, of which 90% is due to metastasis. Cancer is also the major cause of death in Hong Kong and mainland China, and metastasis constitutes ~30% of all death. For example, highly metastatic ovarian tumors are rapidly lethal. At the same time, cancer has been increasingly appreciated as a highly heterogeneous disease, with many different genetic alterations for each cancer patient. It is very challenging to identify the cancer-driving and metastasis-promoting mutation from the large amount of alterations, and it is difficult to correlate the mutations to cancer phenotype. Moreover, the complicate tumor-host interaction in the microenvironment play an important role in metastasis.

The development of therapeutic regimens that will be most effective for cancer patients will first depend on an ability to define the unique characteristics of tumor cell karyotypes and mutations. However, there is a huge knowledge gap from the sequence interpretation to the identification of actionable drug target. We will apply systems biology approaches to holistically examine the complex tumor-host microenvironment interactions, and its implications in cancer metastasis.

Impacts and significance of the research project

Cancer Systems Biology based on interdisciplinary approaches holds promise to help identify the causal mutations and therapeutic targets of cancer. For example, NIH has funded about 10 inter-discipline Cancer Systems Biology Centers at USA to attack this problem. Our group has been employing interdisciplinary approaches combing mathematic modeling with experimental validation to unravel the mechanism underlying tumorigenesis. To dissect the signalling pathway involved in oncogenesis and metastatsis, we have developed a systems biology strategy by integrated analysis of high-throughput data, such as metabolomics, transcriptomics, epigenomics, and proteomics, with bioinformatics and large scale statistical computing (figure 1). This strategy can predict the effects of genetic mutations, environmental and micro-environmental factors on cancer initiation and progression. Successful examples are our key contributions into the establishment of global genetic networks governing early hematopoiesis with insight into the etiology of acute lymphoblastic leukemia associated with the Ikaros and BCR-ABL mutation, the role of microRNAs in tumorgenesis, and functional characterization of single nucleotide polymorphism (SNP). Recently, we have developed some novel and powerful algorithms and software (CMI-GRP, see figure 1) to capture the complicated interaction between signalling pathways involved in oncogenesis. The algorithm, based on information theoretic approaches, can identify genes directly interacting with each other, with elimination of indirect correlation. We can identify critical kinases and phosphatases with regulation by post-translation modification. The software, a R package, can integrate different types of OMICS data. We have also developed a pipeline to build gene network with data mining from Pubmed and other public OMICS databases. In this proposal, we aim to address cancer metastasis with the newest Systems Biology tools developed by us recently, which can not only provide mechanistic insight into cancer metastasis, but can also model the response of anti-cancer drugs.

Currently, many chemotherapeutics use cytotoxic and anti-mitotic drugs. Co-drugging to specifically target the highly evolvable, therapy-resistant polyploids will have great therapeutic significance and may reduce the cell-to-cell variability response. Our findings will have implications for the use of downstream targets as therapeutics. This research is not only relevant to ovarian cancer, but also to other cancers, such as breast, gastric, and colon cancers, of which macrophage cooption is an important pathological process and polyploidization is a common phenomenon.

Objectives

In this proposal, we propose to (i) decipher the molecular mechanism of macrophage-HM interaction-induced polyploidization, (ii) identify the adhesion receptors that mediate the HM-macrophage interaction, and (iii) decipher the effects of polyploidization in the metastatic ability and drug response.

Research Plan and Plan of collaboration

We have derived for the first time a pair of isogenic HM (highly metastatic) and NM (non-metastatic) cells with dramatically opposite metastatic capabilities, though equally tumorigenic. HM was unique in its ability to metastasize consistently to the peritoneum, mimicking a major dissemination route of human ovarian cancer. Conversely, NM did not metastasize. Using this well-controlled system, we have discovered that macrophages supported HM (highly metastatic), but not NM (non-metastatic) tumor cell growth. It is clinically relevant that disseminated cancer cells that succeed in infiltrating the peritoneum specifically adhere on macrophages, whereas those that fail to coopt also fail to thrive. Indeed, a high density of tumor-associated macrophages significantly correlates with poor prognosis. Depletion of macrophages in mice results in reduced metastasis.

Interestingly, this interaction between macrophages and HM induced polyploidy in a significant subset of HM, representing a previously undescribed source of polyploidization. Polyploidy is a well-observed phenomenon in tumors that can actively contribute to tumor growth, heterogeneity, and chemoresistance. The metastatic foci of ovarian carcinoma have the highest number of polyploidy cells, where its presence is associated with poor prognosis. Given the distinct growth and survival advantages of polyploids, further investigations are clearly warranted. Elucidating the molecular mechanisms underlying the regulation of this tumor-macrophage interaction-driven polyploidization and its subsequent phenotypes and fate will conceivably help to develop novel treatment strategies in the future. This work will also lay down the groundwork for a research project with potential for CRF funding.

(i) We will pinpoint the molecular mechanisms that give rise to polyploidy HM cells by examining specifically the mitotic phase of HM in interaction with macrophages. The failure of cell division upon the mitosis-to-interphase transition could be due to either failure of proper bipolar spindle formation or malfunction of the cytokinesis machinery. We will first investigate these two possibilities. Another route to polyploidy is through endoduplication of DNA. In addition, massive chromosome missegregation can induce aneuploidy and genomic/chromosome instability (by using Alice's models and Karen's expertise in cell cycle biology).

(ii) In our pilot study, using next-generation proteomics for in-depth profiling, there was a significant overlap between the HM and a recently described malignant ascites signature of human ovarian cancer, highlighting its clinical relevance and usefulness. Most importantly, we found molecular signature that distinguished HM from NM. This provides a novel and powerful experimental model to evaluate more molecules critically causing metastasis by mediating the tumor-host interaction. We will also be able to use various molecular biology techniques to refine to smaller region and map the motif for binding, to provide a structural basis for mechanistic understanding of the interaction and for exploring therapeutic targeting of the complex (using Jiangwen's expertise in systems biology).

The polyploid fate of HM may provide a selective niche for therapeutic targeting. In yeast, polyploid cells have been shown to have geometric scaling problem in the spindle length, even though the cell volume, centrosome size, and kinetochore number increases. This can lead to improper kinetochore-spindle attachment, sister chromatin cohesion defect and chromosome missegregation in the subsequent mitoses. Moreover, the extra centrosomes in polyploidy cells that arisen from cell division failure also contributes to chromosome instability. On the other hand, understanding the requirement of polyploid cells will enable us to target these tumor cells. Indeed, polyploid cells have increased sensitivity to the microtubule poison benomyl. Aurora B, responsible for correcting improper kinetochore-spindle attachment, is overexpressed in many tumors and is specifically required for polyploid cells for survival. We will

examine the viability, metastatic ability and interaction with macrophage of HM and NM upon polyploidy-specific treatments, such as benomyl and Aurora B inhibitor (using Karen's model organisms and Anderson's expertise in inhibitor/drug kinetics).

This project is developed based on our exciting initial data on tumor-macrophage interaction and polyploidization in the context of the state of the art in the field. All PIs in this proposal have proven experience and track records in carrying out genomic research and cell signaling pathway study.

Budget

Consumables (chemicals and reagenets for cell culturing and small molecule screening) $75,000

Software developments and equipment $75,000

Total $150,000