The 2nd Beijing International Symposium on Tumor Microenvironment

May 30–31, 2013

Tsinghua University, Beijing, China

Abstract

New populations of immunosuppressive cells and their tumor-promoting roles in tumor microenvironment

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Cancer-related inflammation has many tumor-promoting effects, promoting cancer cell proliferation and survival, facilitating angiogenesis and cancer metastasis, suppressing immune responses against cancer. Increasing evidences demonstrate that pro-inflammatory cytokines and immunosuppressive cells are crucial for cancer-related inflammation, which can directly or indirectly promote tumor development and progression. Among of the immunosuppressive cells, myeloid derived suppressor cells (MDSCs), regulatory T cells (Treg), Type 2 macrophages (M2) attach more attraction now. We are wondering whether there exist the unidentified immunosuppressive cell subsets in the tumor microenvironments which may affect the immune response against cancer. Several new kinds of immunosuppressive cell populations have been identified and their underlying mechanisms to promote tumor immune escape and tumor metastasis have been investigated.

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Nucant pseudopeptides as specific antagonists of surface nucleolin inhibit tumor cell growth, adhesion, migration, and/or induce cell death

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Nucleolin is one of the major proteins of the nucleolus, but it is also expressed on the cell surface where is serves as a binding protein for variety of ligands implicated in tumorigenesis and angiogenesis. In contrast to nuclear nucleolin, surface nucleolin is glycosylated and is constantly induced in proliferating tumor and endothelial cells.

Emerging evidence suggests that the cell-surface expressed nucleolin is a strategic target for an effective and nontoxic cancer therapy. In this respect, multivalent HB-19 and related Nucant pseudopeptides (Nucant: N3, N6, N6L and N7) that present pentavalently or hexavalently the tripeptide Lysψ(CH_2N)-Pro-Arg) specifically target the cell-surface expressed nucleolin to mediate inhibition of tumor cell growth *in vitro* and *in vivo* in various mouse models. For example, nucleolin antagonist HB-19 pseudopeptide markedly suppresses the progression of established human breast tumor cell xenografts in the nude mice, whereas in RET mice it delays significantly the onset and frequency of spontaneous melanoma, impairs tumor angiogenesis, and reduces metastasis.

Surface nucleolin exists in a high molecular weight complex, referred to as 500-kDa complex, in association with protein partners known for their implication in cell signalling, tumor cell adhesion, migration, invasion, cell death, autoimmunity, and bacterial infections. As the 500-kDa complex is highly stable, targeting surface nucleolin could change the organization of this complex and thus interfere with the proper functioning of surface nucleolin and the associated proteins. By using HB-19 and related Nucant pseudopeptides we demonstrated that such surface nucleolin antagonists exert distinct inhibitory mechanisms depending on the malignant tumor cell type. For example, in epithelial tumor cells they inhibit cell adhesion or spreading and induce reversion of the malignant phenotype while in leukemia cells they trigger a rapid cell death associated with DNA fragmentation. The inhibitory effect of Nucant pseudopeptides is associated with selective down or up regulation of certain cellular genes. Accordingly, Nucants inhibit expression of specific matrix metalloproteinases in G401 (rhabdoid tumor of the kidney) and TIII (malignant melanoma) cells, whereas in leukemia cells they affect expression of genes implicated in cell death: they induce either enhanced expression of **TNF-α** (tumor necrosis factor alpha) or marked inhibition of Hsp70 expression (the 70 kilo Dalton heat shock protein).

Nucant pseudopeptides represent a unique multi-action drug providing novel therapeutic opportunities in treatment of a wide variety of cancers and related malignancies. As surface nucleolin is continuously and abundantly expressed in tumor compared to normal cells, Nucant pseudopeptides exert their inhibitory effects by targeting preferentially tumor cells. Moreover, Nucant pseudopeptides block the functioning of surface nucleolin without affecting nuclear nucleolin, which is known to control many aspects of normal cell metabolism. Consequently, treatment with Nucant pseudopeptides appears to be devoid of any apparent toxicity *in vitro* and *in vivo*.

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Regulation of central nervous system angiogenesis

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The vasculature of the central nervous system (CNS) develops by sprouting angiogenesis during embryonic development. In adult life, the CNS vasculature exerts significant functions through cerebral perfusion and the blood-brain barrier, whose importance is attested to by pathophysiologic processes such as stroke, multiple sclerosis and cancer. We will review evidence implicating GPR124/TEM5, an orphan G protein-coupled receptor, as an essential regulator of developmental CNS angiogenesis using in vivo gain- and loss-of function analysis. Further, the relevance of GPR124 to adult pathophysiologic processes will be discussed.

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Abstract

Targeting Cancer Epigenetics: from Signals to Chromatin

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It is well established that the small GTPase Ras promotes tumor initiation by activating at least three different mediators: Raf, PI3K, and Ras-like (Ral) guanine nucleotide exchange factors. However, the exact mechanisms that underlie these different Ras signaling pathways, which are involved in tumor progression, remain to be elucidated. We have found that the Ras-PI3K pathway, but not Raf or the Ral guanine nucleotide exchange factors, specifically targets the acetylation of H3 at lysine 56 (H3K56ac), thereby regulating tumor cell activity. We demonstrated that Ras-PI3K regulates H3K56 acetylation (H3K56ac) via the MDM2-dependent degradation of CBP/p300. H3K56 acetylation is a critical component of the oncogenic Ras-PI3K pathway. The Ras-PI3K-AKT-H3K56ac pathway is a potential target for cancer therapy.*(Liu Y et al., J Biol Chem. 2012)*

Besides，we also found that H4K16 acetylation (H4K16ac) is modulated by PI3K signaling in Drosophila melanogaster. Increasing the level of H4K16ac by depleting histone deacetylase 3 (Hdac3) effectively reverses the PI3K-induced tissue overgrowth and alterations in the transcription profile. Hdac3 controls growth through the regulation of H4K16 deacetylation. Alterations in H4K16ac through the ectopic expression of males-absent-on-the-first (MOF), a histone acetyltransferase that specifically targets H4K16, result in changes of cell/body size. Overall, our studies indicated that Hdac3 served as an important regulator of the PI3K pathway and revealed a novel link between histone acetylation and growth control.*(Lv WW et al., J Cell Sci. 2012)*

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Tumor-derived exosomes initiate pre-metastatic niche formation and organ-specific metastasis

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Metastasis is the most deadly aspect of cancer due to a lack of appropriate therapies. Tumor-secreted factors have been recently recognized to be one of the main culprits for metastatic progression. Tumor-secreted factors such as VEGF-A, PlGF, TGFβ, TNF-a, and LOX have been shown to play active roles in the recruitment of bone marrow (BM)-derived cells to the primary tumor microenvironment and pre-metastatic niches. We have found that tumor-derived exosomes are abundantly secreted into the circulation in highly metastatic murine models and in patients with stage IV metastatic disease. Tumor-derived exosomes induce vascular leakiness, hypoxia, and pro-inflammatory changes at pre-metastatic sites. Moreover, tumor-derived exosomes preferentially fuse and "educate" BM-derived progenitor cells to a pro-vasculogenic phenotype characterized by upregulation of Tie-2, VEGF-A, VEGFR2, TSP1 and ADAM10. We found that B16-F10 melanoma-derived exosomes help establish pre-metastatic niches, including the recruitment of "educated" BM cells, in specific organs destined to be involved in future metastasis whereas LLC lung cancer-derived exosomes predominant in the lung as the main organ of metastasis. These results suggest that tumor-derived exosomes may have a role in metastatic organotropism, whereby cancer metastasizes to specific organs, as proposed by Stephen Paget's 'seed and soil' hypothesis more than a 100 years ago. We believe that the identification of exosomes proteins, with their prognostic and therapeutic potential, may also partially explain the specific receptor-ligand binding of exosomes to a pre-metastatic niche defining an organotropic site for future metastasis.

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Potential Therapeutic Targets in Multiple Aspects of Tumor Microenvironment

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Endostatin is a potent endogenous inhibitor of both angiogenesis and lymphangiogenesis. We have reported that cell surface nucleolin is a novel receptor of endostatin, which is specifically expressed on endothelial cell surface of angiogenic blood vessels in tumor tissues. Recently, we have further revealed that endostatin induces the complex formation of nucleolin with integrin α5β1 and urokinase-type plasminogen activator receptor (uPAR) on cell surface. Cholesterol sequestration with nystatin, an anti-fungal drug, manipulates the endocytic routes of endostatin and significantly increases the uptake and efficacy of endostatin in tumors. Additionally, we have further demonstrated that nystatin promotes the uptake of EGFR-targeting agents (including monoclonal antibody and antibody-drug conjugate), resulting in enhanced therapeutic efficacies of these agents in tumors.

Previously we discovered that the CXCL12 (SDF-1α)/CXCR4 axis regulates pericyte recruitment and local vascular remodeling in platelet-derived growth factor-BB (PDGF-BB) overexpressing tumors. Recently we have identified that the CXCL12 (SDF-1α)/CXCR4 axis is a potent positive-regulator of lymphangiogenesis. In addition, targeting both CXCL12 and VEGF-C pathways results in a synergistic inhibitory effect on tumor lymphangiogenesis and lymphatic metastasis. These results demonstrate that the CXCL12 (SDF-1α)/CXCR4 axis is directly involved in both tumor angiogenesis and lymphangiogenesis. The CXCL12 (SDF-1α)/CXCR4 axis may emerge as a potential target for anti-angiogenic and anti-lymphangiogenic therapies which can affect both tumor growth and metastasis.

We have also found that the primary tumor can elicit the destabilization of pulmonary vasculatures and prepare a niche to facilitate distant metastasis, through the upregulation of three proteins including angiopoietin-2, MMP-3, and MMP-10 in the lung. Moreover, our studies on tumor cell-secreted Hsp90α indicate that Hsp90α is a potential biomarker for tumor diagnosis and therapeutic target for tumor therapy. The monoclonal antibody of Hsp90α can be utilized not only in the ELISA diagnostic kit of Hsp90α, but also as a potential therapeutic agent for tumor angiogenesis, progression, and metastasis.

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Abstract

Vasohibin-2 as a novel target for cancer treatment

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The vascular system is one of the most quiescent organs in the body, but has the capacity to form neo-vessels. This process, known as angiogenesis, occurs in various pathologic conditions including cancers. We have isolated vasohibin-1 (VASH1) as a novel VEGF-inducible endothelium-derived angiogenesis inhibitor, and vasohibin-2 (VASH2) as its homologue. We found that VASH1 and VASH2 are highly conserved between species, and their roles in the regulation of angiogenesis are distinct and perhaps contradictory. Our subsequent analyses indicated that VASH1 is expressed in endothelial cells and regulates the course of angiogenesis under pathophysiological conditions including cancers. In contrast, VASH2 is expressed mainly in cancer cells and promotes tumor growth by stimulating angiogenesis. Immunohistological analysis revealed that VASH2 protein was preferentially detected in various human cancers including serous ovarian adenocarcinoma and hepatocellular carcinoma. This expression of VASH2 in cancer cells is mediated not by hypoxia but by the alteration of miR-200b expression. We then used 2 representative human serous adenocarcinoma cell lines, and examined the role of VASH2 in the tumor. The knockdown of VASH2 showed little effect on the proliferation of cancer cells *in vitro*, but notably inhibited tumor growth, peritoneal dissemination, and tumor angiogenesis in a murine xenograft model. Thus, VASH2 can be a potential target for cancer treatment. We have recently developed neutralizing anti-human VASH2 monoclonal antibody. The efficacy of our antibody will be presented in the symposium.

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CCL18-PITPNM3 Signaling Pathway, a Novel Target against both Cancer Cells and Stromal Cells in the Tumor Microenvironment

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Tumor infiltrating leukocytes are key orchestrators of tumor microenvironment directly affecting cancer progression and metastasis. Here, we reported that CCL18 released by tumor associated macrophages promotes the metastasis of cancer cells and recruitment of naïve T lymphocytes, which are converted to regulatory T cells in breast cancer. The CCL18 receptor has long been elusive. Interestingly, immunoprecipitation and liquid chromatographymass spectrometry identified CCL18 interacts with PITPNM3, which has no apparent structural or functional similarity to conventional chemokine receptors. Fraction assay showed that PITPNM3, a molecule with six hydrophilic domains, is an integrated membrane protein. After in vitro cell-free expression, PITPNM3 directly binds to CCL18.CCL18 treatment reduced the intracellular cAMP concentration and enhanced [Ca2+]i mobilization of PITPNM3 expressing HEK293 cells, suggesting Gαi activation in response to CCL18. Furthermore, CCL18 promotes the invasion and metastasis of breast cancer xenografts, whereas suppressing PITPNM3 abrogates these effects. These findings indicate that PITPNM3, a six transmembrane protein associated with G-protein signaling is the receptor of CCL18 and CCL18-PITPNM3 pathway could be a therapeutic target for breast cancer metastasis.

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The Hsp90 machinery – mechanism of a new cancer target

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In the eukaryotic cytosol, Hsp90 is the most complex chaperone machinery. It contributes to the activation or conformational maturation steps of hundreds of specific client proteins. Hsp90 is an essential and abundant protein already under physiological conditions and it is further upregulated and activated upon different stresses. Since cancer cells rely heavily on the Hsp90 machinery, Hsp90 has become an attractive target for therapy. Specific inhibitors of Hsp90 which compete with ATP binding to Hsp90 are in clinical trials as new cancer therapeutics.
ATP is important for Hsp90 function as its binding and hydrolysis generates an ordered sequence of conformational changes in the chaperone protein. The conformational changes are slow and occur on the minutes time scale. This process is strictly regulated at several levels, including posttranslational modifications and a large cohort of co-chaperones. During the chaperone cycle, several complexes are formed which differ in the co-chaperones associated with Hsp90. Our analysis of these complexes revealed that some co-chaperones bind to specific conformational intermediates of the Hsp90 dimer in an asymmetric manner, thus inhibiting or accelerating the cycle at defined positions and setting the stage for the co-chaperone exchange required for the progression of the cycle. Some of the clients of Hsp90 strictly depend on the interaction with Hsp90 for activity, among them steroid hormone receptors and many kinases. Reconstitution of the interaction of Hsp90 with client proteins in vitro using the glucocorticoid receptor (GR) as a model allowed us to define the binding region of GR on Hsp90 and showed that GR interacts with specific conformational states of Hsp90. These results, together with the analysis of co-chaperone interactions, provide a new picture of the chaperone cycle of Hsp90.

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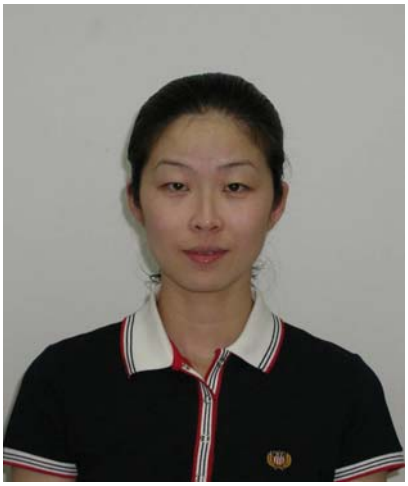
Plasma Hsp90α is a Novel Tumor Biomarker



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Our group has reported the regulatory mechanism of Hsp90α secretion by tumor cells, and the level of plasma Hsp90α is positively correlated with tumor malignancy in cancer patients. These findings provide new targets for cancer therapeutics and suggest Hsp90α as a potential biomarker for tumor diagnosis and prognosis.

Hence, we have developed an ELISA kit for plasma Hsp90α quantification. Clinical trials with the enrollment of 2,347 cases including lung cancer patients, non-cancer pulmonary disease patients, and healthy controls have been accomplished. Diagnostic accuracy of lung cancer was calculated based on the receiver operating characteristics (ROC), and the levels of two well-accepted tumor makers CEA and CYFRA21-1 were assessed in parallel. In the condition-monitoring test of lung cancer patients, levels of plasma Hsp90α decrease constantly upon effective treatments, and increase obviously with disease progression, which indicates that Hsp90α is also a sensitive biomarker for timely efficacy evaluation of cancer therapeutics. These results demonstrate that Hsp90α is a novel tumor biomarker not only for auxiliary diagnosis of lung cancer, but also for efficacy monitoring of anti-tumor therapeutics. This quantitative ELISA kit of Hsp90α has just been approved by China Food and Drug Administration (CFDA) to be used in lung cancer patients. The data will be presented.

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Abstract

The Hippo-YAP pathway in organ size control and tumorigenesis

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The Hippo pathway is crucial in organ size control and its dysregulation contributes to tumorigenesis. Previous studies have revealed regulation of this pathway by cell-cell contact. Here we report that the Hippo pathway is regulated by G-protein coupled receptor (GPCR) signaling. Serum-borne lysophosphatidic acid (LPA) and sphingosine 1-phosphophate (S1P) act through G12/13 coupled GPCRs to inhibit the Hippo pathway kinases Lats1/2, thereby activating YAP/TAZ transcription co-activators. Activation of YAP/TAZ is involved in LPA-induced gene expression, cell migration and proliferation. Thrombin also activates YAP/TAZ by stimulating GPCR signaling. Interestingly, stimulation of Gs coupled receptors by glucagon or epinephrine inhibits YAP/TAZ by activating Lats1/2 kinase. Thus, GPCR signaling can either activate or inhibit the Hippo-YAP pathway in a manner depending on the coupled G-proteins. The cross talk between Hippo and other intracellular signaling pathways will be discussed. Our study identifies extracellular diffusible signals that modulate the Hippo pathway activity and also establishes the Hippo-YAP pathway as a critical signaling branch downstream of GPCR.

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Hypoxia microenvironment and cell metabolism

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One of the central characterictics of tumor microenvironment is the low oxygen status, or hypoxia, which induces the expression of hypoxia inducible factor 1 (HIF1),a master regulator of cancer cells' adaptation to hypoxic stress. It's well established now that HIF1-mediated pathway has been largely responsible for the development of various human malignancies.We and others have uncovered that HIF1 has been important in regulating cancer cell glucose metabolism, so called aerobic glycolysis, or Warburg Effect. Recently, we found that hypoxia microenviroment and HIF1 can enhance breast cancer metastasis by promoting extravasation and metastatic nitch formation throught different mechanisms.

Since HIF1 plays very important roles in cancer development and it is highly expressed in cancers because of the low oxygen microenvironment, it's believed that targeting HIF1 pathway may provide noval strategies for cancer therapy. Thus, our effort in screening for HIF1 inhibitors for cancer therapy will also be discussed.

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Abstract

A novel gene CREPT promoting tumorigenesis by regulating Cyclin D1 expression via a chromatin loop formation

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We have cloned a novel gene *CREPT* (*C*ell-cycle *R*elated and *E*xpression-elevated *P*rotein in *T*umor) based on a homology screen using p15RS, which contains a RPR domain (regulation of nuclear pre-mRNA, or CID, CTD-interacting domain). Human CREPT shares a high similarity of amino acids to p15RS. Our previous studies revealed that p15RS negatively regulates Cyclin D1 expression, functioning as an intrinsic inhibitor for the canonical Wnt/β-catenin signal pathway. We found that p15RS inhibits cell growth and Wnt targeted gene expression by blocking the interaction of β-catenin and TCF4 in the nucleus. Interestingly, when we over-expressed CREPT we observed that cell proliferation was enhanced and the expression of cell cycle related genes including Cyclin D1 was up-regulated. We further demonstrated that CREPT regulates Cyclin D1 expression by binding to its promoter, enhancing its transcription both in vivo and in vitro, and interacting with RNA polymerase II (RNAPII). Interestingly, CREPT promotes the formation of a chromatin loop and prevents RNAPII from reading through the 3'-end termination site of the gene. Finally, we observed that CREPT is highly expressed in human tumors and the positive CREPT staining is significantly correlated with shorter survival time of the patients after surgery and treatment. Our findings reveal a novel mechanism where CREPT increases cyclinD1 transcription during tumorigenesis, through enhancing the recruitment of RNAPII to the promoter region, possibly, as well as chromatin looping. We expected that CREPT might be another marker for prognosis and a potential target for the development of anti-caner drugs.