Ninth AACR-Japanese Cancer Association Joint Conference:

BREAKTHROUGHS IN BASIC AND TRANSLATIONAL CANCER RESEARCH

February 21-25, 2013
Hyatt Regency Maui
Maui, HI

Conference Co-Chairpersons:

Tyler Jacks
David H. Koch Institute for Integrative
Cancer Research at MIT, Cambridge, MA, USA

Kohei Miyazono
University of Tokyo, Tokyo, Japan

Program and Proceedings

AACR American Association for Cancer Research

JCA JAPANESE CANCER ASSOCIATION

Program

3:30 p.m.-5:00 p.m. **Session 6: Cancer Progression and Metastasis**
Monarchy Ballroom
Co-Chairpersons: Motoharu Seiki, University of Tokyo Institute of Medical Science, Tokyo, Japan, and Lynda Chin, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

3:30 p.m. **Molecular characterization of lung cancer progression***
Tyler Jacks, David H. Koch Institute for Integrative Cancer Research at MIT, Cambridge, MA, USA

4:05 p.m. **Hypoxia-inducible factor activity is an excellent marker for tumorigenesis and cancer progression***
Shinae Kondoh, Tokyo Institute of Technology, Tokyo, Japan

4:40 p.m. **The systemic environment as an important determinant of malignancy**
Sandra S. McAllister, Brigham and Women's Hospital, Boston, MA, USA

5:00 p.m.-7:00 p.m. **Poster Session B**
Regency Ballroom and Grand Promenade

Sunday, February 24

7:00 a.m.-8:00 a.m. **Breakfast/Mentoring Roundtables**
Sunset Terrace

8:00 a.m.-9:30 a.m. **Session 7: Tumor Microenvironment**
Monarchy Ballroom
Co-Chairpersons: Kevin M. Haigis, Massachusetts General Hospital, Charlestown, MA, USA, and Atsushi Ochiai, National Cancer Center, Hospital East, Kashiwa, Japan

8:00 a.m. **Molecular targeting of tumor vasculature***
Gou Young Koh, Korea Advanced Institute of Science and Technology (KAIST), Daejeon, Korea (Rep.)

8:35 a.m. **Inflammation and cancer: Reprogramming the immune microenvironment as an anticancer therapeutic strategy***
Lisa M. Coussens, Oregon Health and Science University's Knight Cancer Institute, Portland, OR, USA

9:10 a.m. **Mint3 promotes tumor malignancy in cancer and stromal cells***
Takeharu Sakamoto, University of Tokyo, Institute of Medical Science, Tokyo, Japan

*An extended abstract for this presentation is available in the Invited Abstracts section of the *Proceedings*.

detected by noninvasive bioluminescence imaging in tissues that contained papillomas and malignant lesions. These results strongly suggest that HIF activity is an excellent marker for multiple steps of carcinogenesis. Therefore, early detection of HIF-active regions is important for initiating timely and appropriate cancer treatment.

We have been developing an anti-cancer drug and diagnostic probes for HIF-active tumors by using fusion proteins containing PTD-ODD. A protein transduction domain (PTD) allows a whole protein to efficiently penetrate cell membranes and spread throughout the body. An oxygen-dependent degradation (ODD) domain is derived from human HIF-1α; and PTD-ODD fusion proteins are under the same ODD regulation as HIFα; the PTD-ODD proteins are quickly degraded in HIF-inactive [HIF(-)] cells, while degradation is suppressed in HIF-active [HIF(+)] cells, allowing the PTD-ODD proteins to accumulate in HIF(+) cells. By using in vivo optical imaging system, we have proved that the PTD-ODD proteins are able to target and image HIF-active tumors.

Session 7: Tumor Microenvironment

IA22 Molecular targeting of tumor vasculature. Gou Young Koh. KAIST, Daejeon, Korea (Rep.).

Tumor vasculature consists of destabilized, malformed, enlarged, leaky and highly branched vessels which continuously undergo vascular remodeling. These features are mainly attributed to abnormally high VEGF-A levels in the tumor microenvironment, and blockade of VEGF-A has indeed been shown to suppress the pathological characteristics of tumor vessels. However, blockade of VEGF-A/VEGFR2 signaling can often promote rebound hypoxia, micro-invasion, drug-resistance and metastasis, all of which make treating cancers with current anti-angiogenic therapies particularly challenging. Since angiopoietin-2 (Ang2) plays a supportive role in VEGF-A-induced pathological vascular remodeling and Ang2 levels are high in the tumor microenvironment, single blockade of Ang2 or simultaneous blockade of VEGF-A and Ang2 are currently being tested in experimental and clinical settings. Nevertheless, anti-angiogenic therapy against tumor progression still seems ineffective and limited in clinics. Here, we found that RhoX, one of Rho family proteins, is selectively expressed in endothelial cells of tumor vessels, and plays a central role in vessel stabilization. Compared to control mice, RhoX-deficient mice showed delayed tumor progression, reduction of vascular density and tumor metastasis in the xenograft and primary tumor animal models. The RhoX-deficient mice strikingly displayed severe vascular leakage and tumor necrosis, which could be due to marked drop-out of perivascular cells and profound shut-down of tumor vessels. Specific aptide-liposomal delivery of siRNA targeting RhoX could recapitulate the antitumor effect and the vascular shut-down effects shown in RhoX-deficient mice. More importantly, blockade of VEGF-A/VEGR2 signaling by administration of VEGF-Trap to RhoX-deficient mice showed almost complete suppression of tumor progression and metastasis without any potentiation of side effects. Our data collectively suggest that concomitant blockade of VEGF-A and RhoX could serve as a novel and effective targeting method (or approach) for dual suppression and shut-down of tumor vasculature.

IA23 Inflammation and cancer: Reprogramming the immune microenvironment as an anticancer therapeutic strategy. Lisa M. Coussens. Knight Cancer Institute, Oregon Health & Science University, Portland, OR.

The concept that leukocytes are components of malignant tumors is not new; however, their functional involvement as promoting forces for tumor progression has only recently been appreciated. We are interested in understanding the molecular mechanisms that regulate leukocyte recruitment into neoplastic tissue and subsequent regulation those leukocytes exert on evolving cancer cells, and how malignant cells in turn respond to cytotoxic therapies. By studying