「金沢大学重点戦略経費政策課題対応型研究推進セミナー」を開催

2011 年 10 月 6 日

10月6日（木）にがん進展制御研究所棟4階　会議室において，台湾国立陽明大学　Kou-Juey Wu特別教授を迎え，「The role of chromatin modifiers in hypoxia-induced epithelial-mesenchymal transition (EMT)」と題して，腫瘍分子生物学セミナーを開催しました。

セミナーでは，Kou-Juey Wu先生ご自身の最新の研究成果を示されながら，がんの浸潤・転移やがん幹細胞成立の基盤となる上皮間葉転換(EMT)の分子メカニズムについて，大変興味深いご講演を頂きました。

セミナーには，所内外の研究者並びに大学院生ら約40名が参加し，活発な質疑応答や意見交換が行われました。

腫瘍分子生物学セミナー

日時：平成２３年１０月６日　１６時より
場所：がん進展制御研究所４階　会議室

演題：**The role of chromatin modifiers in hypoxia-induced epithelial-mesenchymal transition (EMT)**

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Epithelial-mesenchymal transition (EMT) is important for organ development, metastasis, cancer stemness, and organ fibrosis . Tumor hypoxia is linked to tumor progression and hypoxia-inducible factor-1 (HIF-1) directly or indirectly regulates the expression of different EMT regulators. We previously showed that hypoxia induced Twist1 expression to promote metastasis [1]. EMT induces stem-like properties in epithelial cells. Bmi1 is a polycomb group protein which maintains self-renewal and it is frequently overexpressed in human cancers. Here we show the direct regulation of *Bmi1* by the EMT regulator Twist1. Moreover, Twist1 and Bmi1 were mutually essential to promote EMT and tumor-initiating capability. Twist1 and Bmi1 acted cooperatively to repress both *E-cadherin* and *p16INK4A*. In patients with head and neck cancers, only co-overexpression of Twist1 and Bmi1 correlated with downregulation of both E-cadherin and p16INK4A, and was associated with the worst prognosis. These results provide a critical mechanism of Twist1-induced EMT and tumor-initiating capability in cancer cells through chromatin remodeling, leading to unfavorable clinical outcomes [2].

The molecular mechanisms to coordinately regulate hypoxia-induced EMT remain elusive. The chromatin modifiers which coordinate the regulation of hypoxia-induced EMT marker gene expression were not identified. Here we show that HIF-1α-induced *histone deacetylase 3* (*HDAC3*) is essential for EMT and metastatic phenotypes. Change of specific chromatin states is associated with hypoxia-induced EMT. Under hypoxia, HDAC3 recruits hypoxia-induced WDR5/HMT (histone methyltransferase) complex and associates with mesenchymal gene promoters to increase H3K4-specific HMT activity and activate mesenchymal gene expression. HDAC3 also serves as an essential co-repressor to repress epithelial gene expression. Knockdown of WDR5 abolishes mesenchymal gene activation but not epithelial gene repression during hypoxia-induced EMT. These results indicate that hypoxia induces different chromatin modifiers to coordinately regulate EMT through distinct mechanisms [3].

References:

1. Nature Cell Biology 2008; 10,295-305.
2. Nature Cell Biology 2010; 12,982-992.
3. Molecular Cell 2011; 43, 811-822 (Sept. 2, Featured Article).

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