Direct Activation of Bmi1 by Twist1: Implications in Cancer Stemness, Epithelial-Mesenchymal Transition, and Clinical Significance

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Cancer stemness is a concept used to describe a minor population of cells (cancer stem cells-CSCs) residing in a tumor, which possess self-renewal properties and are resistant to chemo/radiation therapy. Epithelial-mesenchymal transition (EMT), a major mechanism of cancer metastasis, is a process which generates cells with stem-like properties. The relationship between cancer stemness and EMT is well documented but without detailed mechanistic explanation. Bmi1 belongs to the polycomb repressive complex 1 (PRC1) which maintains self-renewal and stemness. Recent results showed that Twist1, an EMT regulator, directly activates Bmi1 and these two molecules function together to mediate cancer stemness and EMT. These results provide a molecular explanation of the relationship between cancer stemness and EMT. Bmi1 is frequently overexpressed in various types of human cancers and can confer drug resistance. Twist1 is also overexpressed in various human cancers with prognostic significance. The functional interdependence between Twist1 and Bmi1 provides a fresh insight into the molecular mechanism of EMT-induced cancer stemness. Further investigation of the mechanisms mediating EMT and cancer stemness will be helpful in the management and treatment of metastatic cancers. *(Chang Gung Med J 2011;34:229-38)*

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Cancer stemness is a concept recently proposed to explain cancer cells' resistance to conventional chemo/radiation therapy.[1] Cancer stem cells (CSCs) are described as a small percentage of cells residing in a tumor, which are able to self-renew and have stem-like properties.[1-3] Stem-like properties are monitored by different assays such as staining of surface markers, *in vitro* sphere formation, resistance to chemotherapeutic agents or radiation, *in vivo* tumor-initiating capability, and other assays.[1,4]

Epithelial-mesenchymal transition (EMT) is an important process by which epithelial cells are converted to mesenchymal cells during embryonic development.[5-7] This process involves loss of cell polarity, decrease in cell-to-cell adhesion, and gain of migration ability.[5-7] EMT is also the critical event

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for tumor metastasis and organ fibrosis.[5-7] Repression of epithelial markers (e.g., E-cadherin, plakoglobin and desmoplakin) and upregulation of mesenchymal markers (e.g., vimentin, fibronectin and N-cadherin) are the typical marker changes observed during the EMT process.[5-7] Different transcription factors such as Snail (also known as SNAI1), Slug (also known as SNAI2), Zeb1 (also known as TCF8 and δEF1), SIP1 (also known as Zeb2 and ZFXH1B), E47 (also known as TCF3), and Twist1 are termed "EMT regulators" since they were shown to regulate EMT.[8-13] In spite of the demonstration of the role of EMT in embryonic development, cancer metastasis, and organ fibrosis, it is unknown whether EMT plays a significant role in other aspects of cell biology.

This review summarizes recent findings in the relationship between cancer stemness and epithelial-mesenchymal transition, the regulation of *Bmi1* by Twist1 and its significance in cancer stemness, and the role of Bmi1 and Twist1 in contributing to various types of human cancers.

The relationship between cancer stem cells and epithelial-mesenchymal transition

The cancer stem cells possess the ability to self-renew and generate secondary tumors, which is described as a "tumor-initiating ability" and is best assayed by *in vivo* limiting dilution assays.[4] It is hypothesized that solid tumors are hierarchically organized and sustained by cancer stem cells.[14] For example, after treatment of breast cancer, the surviving residual tumor cells may be enriched for subpopulations of cells (e.g. CD44+/CD24- or low) with both tumor-initiating and mesenchymal features.[15] Different developmental pathways such as hedgehog, epidermal growth factor receptor (EGFR), Wnt/β-catenin, Notch, polycomb (Bmi1), stromal cell derived factor-1 (SDF-1)/chemokine receptor-4 (CXCR4), PTEN, BMP, and TGF-β were shown to be associated with tumor-initiating abilities.[16] In addition, various cancer subtypes may have different subsets of tumor-initiating cells. For example, CSCs could be isolated or monitored by different cell-surface marker profiles in various types of human cancers (e.g. CD133 in brain, colon, pancreas, lung, and ovarian cancers; CD44 in breast and head and neck cancers).[4] CSCs are associated with a specific state of differentiation (e.g. mesenchymal features).[17]

The EMT process in tumor cells usually results in cells becoming more invasive, metastatic, and drug resistant, which will lead to the subsequent demise of cancer patients.[5-7] It is well documented that EMT will induce tumor progression and aggressiveness.[5-7] EMT-derived cells exhibit multi-lineage differentiation potential similar to mesenchymal stem cells.[18] However, the mechanisms delineating the connection between EMT and cancer stemness are largely unknown. Recent evidences suggest that the process of EMT generates cells with stem-like properties.[19] The earliest example is the generation of proliferative human islet precursor cells during EMT.[20] Loss of p21CIP1 is associated with the generation of breast cancer stem cell properties.[21] Other examples include the demonstration that the EMT process generates stem-like properties in breast cancer cells.[22,23] Since cancer stem cells may have characteristics different from the original tumor cells, or the tumor cells sensitive to chemo/radiation therapy, the link between EMT and cancer stemness provides the explanation that EMT induces tumor progression through induction of cancer stemness.[24-26]

Bmi1, a polycomb protein, regulates and maintains stemness features

Polycomb group (PcG) proteins are chromatin modifiers involved in the maintenance of embryonic and adult stem cells and cancer formation.[27-33] Polycomb group proteins are multimeric transcriptional repressor complexes including polycomb-repressive complex 1 (PRC1) and polycomb-repressive complex 2 (PRC2).[27-33] Polycomb group proteins can occupy the promoters of developmental regulators, and silencing of these genes confers stemness in a PcG-dependent manner.[27-33]

Bmi1 is a member of polycomb-repressive complex 1 (PRC1) which maintains chromatin silencing.[34] Bmi1 was first shown to collaborate with c-Myc to promote lymphomagenesis and regulate cell proliferation and senescence through inhibiting the *INK4A* locus, demonstrating its role as an oncogene.[35,36] Bmi1 was subsequently shown to be required to maintain normal and leukemic hematopoietic stem cells and was essential in the lineage specification and multipotency of hematopoietic stem and progenitor cells.[37-39] In addition, Bmi1 was shown to be involved in the self-renewal of mammary epithelium, neuronal, pancreatic (includ-

ing β-cell), and intestinal cells through repressing the *INK4A-ARF* locus.[40-47] However, repression of *INK4A-ARF* by Bmi1 is dependent on the polycomb-repressive complex 2 (PRC2).[48] After PRC2 binds to the promoters of target genes, EZH2 (a member of PRC2 with histone H3 methyltransferase activity) methylates lysine 27 of histone H3 (H3K27).[49,50] The trimethylated H3K27 (H3K27me3) is then recognized and bound by PRC1.[51] Both PRC1 and PRC2 bind to the promoters of target genes to maintain their repression. Among the target genes of PRC1 and PRC2, repression of the *INK4A*/*ARF* locus is essential for PRC complexes to maintain stemness.[52,53]

Direct regulation of *Bmi1* by Twist1: implications in cancer stemness induced by epithelial-mesenchymal transition

Twist1, a bHLH transcriptional factor, was first demonstrated for its critical role in the *Drosophila* mesoderm development.[54,55] Twist1 governs cell movement and tissue reorganization during early embryogenesis and is a master regulator of gastrulation, mesoderm differentiation, and somatic muscles patterning and specification.[56] The critical role of Twist1 in cancer metastasis was recently demonstrated by the results of increased expression of Twist1 in human cancers, induction of EMT by Twist1, and the association of Twist1 with a more aggressive phenotype and a worse outcome.[10,57] Twist1 expression is triggered by different upstream signaling pathways.[58] We previously demonstrated that hypoxia inducible factor-1 (HIF-1) directly regulates *Twist1* expression.[59] Recent results also identified a subpopulation of highly tumorigenic cells in head and neck squamous cell carcinoma (HNSCC) with stem-like properties and overexpressing Bmi1.[60] Due to the link between EMT and cancer stemness, we hypothesized that Twist1 may induce the expressions of stemness genes, resulting in the promotion of EMT and tumor-initiating ability. Through the screening of possible activation of different stemness genes, a tight correlation between Twist1 and Bmi1 was observed.[61] Different assays such as transient transfection, electrophoretic mobility shift assay (EMSA), and chromatin immunoprecipitation (ChIP) assays were subsequently performed to demonstrate the direct activation of *Bmi1* expression by Twist1. Overexpression of Twist1 or Bmi1 conferred stem-like properties and induced EMT in head and neck cancer cell lines. Bmi1 was critical for Twist1 induced stem-like properties and EMT since knockdown of Bmi1 in Twist1-overexpressing cells abolished both stem-like properties and EMT. Overexpression of Bmi1 alone could induce EMT. Twist1 was also critical for Bmi1-induced stem-like properties and EMT since knockdown of Twist1 in Bmi1-overexpressing cells reversed EMT and abolished stem-like properties. Quantitative chromatin immunoprecipitation (qChIP) assays were performed to test the binding of these two proteins on both *E-cadherin* and *p16INK4A* promoters when either Bmi1 or Twist1 was knocked down. The results showed the functional interdependence of Twist1 and Bmi1 to mediate stem-like properties and EMT since knockdown of either molecule caused the decreased binding of the other molecule on both promoters. Since repression of *E-cadherin* by Twist1 was not shown previously,[7] we further mapped three E-box sites located in the *E-cadherin* promoter responsible for Twist1-induced repression by mutagenesis analysis of these three E-box sites. Electrophoretic mobility shift assay (EMSA) followed by supershifting with the anti-Twist1 or anti-Bmi1-specific antibody showed the co-occupancy of the *E-cadherin* promoter by Twist1 and Bmi1. The essential role of EZH2 was also demonstrated using the assays mentioned above,[61] which was consistent with the reported result.[62] Chromatin immunoprecipitation assays showed the direct binding of Twist1 to the *Bmi1* promoter. Co-immunoprecipitation assay showed the interaction between Twist1 and Bmi1. Our results present the first molecular demonstration of simultaneous repression of both *E-cadherin* and *p16INK4A* expression by Twist1 (an EMT regulator) and Bmi1/EZH2 (components of the polycomb group proteins). These results provide one of the first molecular delineations of the link between cancer stemness and EMT.[61] Transcriptome profiling analysis also showed that head and neck cancer cell lines overexpressing Twist1 or Bmi1 had the transcriptome drifting to the mesenchymal stem cell signatures, but not drifting to the epithelial transcriptome signatures.[61] This result is consistent with the reported result that cancer stem cells display mesenchymal features.[17] Finally, the important role of Bmi1 in cancer stemness is supported by the recent result that Bmi1 was critical in the maintenance of prostate can-

cer stem cells.[63]

Cancer stemness, Bmi1, and drug resistance

Tumor- and metastasis-initiating cells usually develop treatment resistance, which is shown in recurrent ovarian cancer.[64] Activated CD8 T cells can stimulate mammary tumor cells to go through EMT and increase their tumor-initiating ability and chemotherapeutic resistance.[65] Bmi1 is shown to confer different kinds of resistance (radiation, 5-fluorouracil, docetaxel) in different cancers.[66-68] Recruitment of the DNA damage response machinery is shown to cause Bmi1-induced radiation resistance.[69] The detailed molecular mechanisms of treatment resistance are still largely unknown. Future experiments to dissect the signaling pathways regulating different kinds of treatment resistance will require intensive investigation. Finally, the observation and concept of cancer stem cells could mimic the "minimal residual disease" constantly mentioned during the treatment course of certain leukemias.[70]

Expression of Twist1 and Bmi1 and their contribution to clinical significance

Bmi1 overexpression is shown in various cancers such as chronic myeloid leukemia, multiple myeloma, head and neck squamous cell carcinoma, squamous cell carcinoma of the tongue, breast cancers, non-small cell lung cancer, hepatocellular carcinoma, gastric carcinoma, Ewing sarcoma, colon cancer, bladder cancer, esophageal cancer, cholangiocarcinoma, ovarian cancer, endometrial cancer, cervical cancer, and medulloblastoma.[71-95] Bmi1 cooperates with H-Ras to induce aggressive breast cancer.[96] Bmi1 collaborates with BCR-ABL or interacts with PLZF/RARA to mediate leukemic transformation.[97,98] Finally, Bmi1 induces apoptotic resistance through activation of the IKK-NF-kB pathway.[99] The prognostic impact of Twist1 was demonstrated in various cancers,[10,59,100-116] but the interdependence between Twist1 and Bmi1 has never been explored. The cooperative role between Twist1 and Bmi1 was demonstrated in HNSCC cases since only co-overexpression of both proteins correlates with repression of *E-cadherin* and *p16INK4A* and the worst prognosis of HNSCC patients.[61] Patients expressing either Twist1 or Bmi1 alone have a better prognosis than those co-expressing both proteins. This observation further strengthens the model that Twist1 and Bmi1 interdependently promote EMT and cancer stemness, resulting in an aggressive tumor behavior and a dismal outcome in HNSCC.[61] Further confirmation of this functional interdependence will require examination of more tumor samples from various tumor types.

Conclusions and future perspectives

Different mechanisms such as chromatin modification (e.g. promoter hypermethylation) and recruitment of chromatin modifiers such as HDAC1/HDAC2, AJUBA/PRMT5, or PRC2 by EMT regulators were shown to mediate *E-cadherin* repression.[117-119] However, there was no previous demonstration of the involvement of PRC1 complex in the repression of *E-cadherin*. In spite of the repeated demonstrations that *p16INKA* is regulated by Bmi1,[35,36,47] the involvement of an EMT regulator in the repression of *p16INK4A* was not shown. Our results are the first demonstration of the requirement of an EMT regulator and PRC1/2 complexes to simultaneously repress *E-cadherin* and *p16INK4A*. The simultaneous requirement of transcription regulators and chromatin modification complexes (PRC1 and PRC2 in our case) to mediate E-cadherin and *p16INK4A* repression provides a mechanistic example of the relationship between EMT and cancer stemness.

Bmi1 is well documented to maintain stemness.[34,37-39] Twist1 and Twist2 also override oncogene-induced premature senescence in cancer cells by inhibiting the activity of *p16INK4A* and *p21CIP1*.[120] From our results, it appears that Bmi1 acts together with Twist1 to carry out multiple functions, including EMT induction and escape from oncogene-induced premature senescence. Other functions such as induction of telomerase activity, inhibition of TGF-β signaling, and repression of PTEN tumor suppressor were also mediated by Bmi1,[121-123] which may contribute to Bmi1-mediated functions.

In conclusion, the relationship between cancer stemness and EMT is well established. Our demonstration that Twist1 activates Bmi1 and both molecules function interdependently to mediate cancer stemness and EMT provide a molecular delineation of the relationship between cancer stemness and EMT. Investigation of the regulation of Bmi1 or other stemness genes through different mechanisms

should be the subject which needs immediate attention to further explore this relationship. The information obtained from these investigations will be valuable for the management and treatment of metastatic cancers.

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Twist1 直接活化 Bmi1 基因的表達：對癌症幹細胞特性，上皮細胞—間質細胞轉化，及臨床癌症的重要性

吳國瑞

癌症幹細胞的觀念可用來描述一小群存在腫瘤中具有幹細胞特性的癌細胞。癌症幹細胞具有自我更新的能力並且可以抵抗化療和輻射治療。上皮細胞—間質細胞轉化是癌症轉移的重要機制，此過程讓癌細胞具有幹細胞特性。然而上皮細胞—間質細胞轉化和癌症幹細胞的產生兩者間的關係目前並沒有詳細的機制可以解釋。Bmi1 是 polycomb repressive complex 1 (PRC1) 之一員。Bmi1 的功能在於可以維持自我更新能力和幹細胞特性。目前研究指出上皮細胞—間質細胞轉化調控分子 Twist1 可以直接活化 Bmi1 基因的表達，這兩個分子須互相依存進而共同調控上皮細胞—間質細胞轉化和癌症幹細胞特性。這個結果可以解釋上皮細胞—間質細胞轉化和癌症幹細胞特性兩者的關係。Bmi1 大量表現於人類的各種癌症，並且讓癌細胞具有抗藥性。Twist1 也大量表現在人類的各種癌症並且可做爲預測病人預後的標記。Twist1 和 Bmi1 功能性的互相依存與交互作用提供解釋上皮細胞—間質細胞轉化進而誘導癌症幹細胞特性一個嶄新的概念。未來進一步探討上皮細胞—間質細胞轉化誘導癌症幹細胞特性的機制可以對轉移性癌症的處理及治療有更顯著的貢獻。(長庚醫誌 2011;34:229-38)

關鍵詞：上皮細胞—間質轉化，癌症幹細胞，癌症轉移，Twist1，Bmi1

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