PREFACE: Contrasting Roles of KLF4 as an Oncogene or Tumor Suppressor

The highly focused special section on the contrasting roles of the transcription factor KLF4 as either a tumor suppressor or oncogene in various cancers has been a challenge regarding the underlying mechanisms of those contrasting activities and their implications as both biomarkers and therapeutic targets. KLF4 is also a pleiotropic gene product that has been reported to have an important role in cancer stem cells. This issue consists of eight chapters that deal specifically with the various parts that KLF4 plays in many cancers and provides a general overview of its clinical significance.

Walden Ai's *Role of Immune-Cell–Expressing Kruppel-Like Factor 4 in Cancer Development* reviews the roles and functions of KLF4 in both immune cells and cancer stem cells. The correlation between KLF4 expression and its action as an oncogene or tumor suppressor was suggested to be a result of the existence of KLF4 isoforms and that the ratios of expression levels of the different isoforms may dictate the outcome in tumor development. In addition, Dr. Ai suggests that the role of KL4 as an oncogene or tumor suppressor may also relate to the differentiation of the cancer epithelial cells. Additional studies also revealed that immune cells that also express KLF4 contribute to tumor development.

Moyal et al.'s *Identification of the Alternating Oncogenic and Tumor-Suppressor Activities of Kruppel-Like Factor 4 in Various Human Cancers* reports on the classification of the majority of cancers whose KLF4 expression levels correlate with either tumor suppressor or oncogenic properties. The analysis was a composite of bioinformatics data on mRNA levels of KLF4 as well as literature-reported data on KLF4 protein expression in various cancers. The analyses indicated that in the majority of cancers, KLF4 was overexpressed and acted as an oncogene, whereas in a minority of cancers, KLF4 levels were low, thus acting as a tumor suppressor. The data analyses provided new insights into the role of KLF4 as a potential prognostic marker as well as a therapeutic target that uses agents that either activate or repress KLF4, depending on its activity as a tumor suppressor or oncogene, respectively.

Yang and Zheng's *Dual Roles of KLF4 as a Tumor Suppressor or Oncogene* discusses the duality of KLF4 as a tumor suppressor or oncogene and the possible role of cyclin-dependent kinase inhibitor 1 (p21) as a possible gene product that is involved in switching the functions of KLF-mediated signaling, resulting in KLF4 behaving as a tumor suppressor or oncogene. They also suggest the potential role of inactivating KLF4 as a new therapeutic.

Wottrich and Bonavida's *Regulation of the Cancer Stem Cell Phenotype by Raf Kinase Inhibitor Protein Via Its Association with Kruppel-Like Factor 4* reports on the linkage between KLF4 and Raf kinase inhibitor protein (RKIP) expressions in cancers and, particularly, in cancer stem cells. A detailed analysis is presented on the interrelationship between KLF4 and RKIP in cancer stem cells and, particularly, on the interrelationship of cancer stem cell transcription factors and other factors that have been reported to induce the cancer stem cell phenotype. Clearly, such interrelationships must be followed by experimental validation.

Yue et al. report on *Kruppel-Like Factor 4 in Ovarian Cancer*. In contrast to many other cancers, in ovarian cancer, KLF4 expression acts as a tumor suppressor by inhibiting cell proliferation, migration, invasion, and metastases. These researchers report on the binding of KLF4 on the E-cadherin promoter, activating its expression and inhibiting the cancer stem cell phenotype in ovarian cancer. They suggest that KLF4 expression is a prognostic biomarker as well as a therapeutic target in ovarian cancer and discuss various microRNAs that target KLF4 and regulate its expression. KLF4 inhibits the expression of many microRNAs, resulting in the inhibition of the epithelial-to-mesenchymal transition. These researchers also suggest the potential use of the KLF4 inducer APTO-253 in clinical studies

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in patients with ovarian cancer. Alternatively, they propose the use of lentil viral or adenoviral vectors for KLF4 overexpression as therapy.

Ray's *The Transcription Regulator Kruppel-Like Factor 4 and Its Dual Roles as Oncogene in Glioblastoma and Tumor Suppressor in Neuroblastoma* describes the oncogenic role of KLF4 in glioblastoma and its tumor-suppressor role in neuroblastoma. The survival of glioblastoma stem cells is dependent, in part, on KLF4; thus, KLF4 acts as an oncogene and participates in the regulation of the cancer stem cell phenotype. A high level of KLF4 expression is associated with poor outcomes in glioblastoma patients. In contrast, in neuroblastoma, KLF4 acts by inhibiting the cell cycle and activating cell differentiation and cell death pathways. Low expression of KLF4 is associated with poor prognosis in neuroblastoma patients. Here again, KLF4 is a significant therapeutic target in addition to its having prognostic significance.

Morales et al.'s *Bifunctional Role of Kruppel-Like Factor 4 in Hematological Malignancies* reports on the role of KLF4 expression in hematological malignancies. Discussed is the discrepancy between adult lymphomas, wherein KLF4 is considered to be a tumor suppressor, and pediatric lymphomas, in which KLF4 expression is high and acts as an oncogene. These authors report that the overexpression of KLF4 in pediatric non-Hodgkins lymphoma predicts unresponsiveness to cyclophosphamide, doxorubicin hydrochloride, vincristine, and prednisone (referred to as CHOP) treatment in these patients. In addition, they examine the relationship between the Ying Yang-1 (YY1) transcription factor, resistant factor, and KLF4 in both tumor cell lines and patient-derived lymphoma tissues. They report on the transcriptional regulation of KLF4 by YY1 and suggest that both are potential biomarkers and therapeutic targets.

Zhao et al.'s *Kruppel-Like Factor 4: From Physiological Functions to Tumor Therapy* review the physiological functions of KLF4 in solid cancers and leukemias. These authors describe several biological mechanisms in which KLF4 affects gene products involved in cell proliferation and cell death and illustrate the molecule APTO-253 to be a chemical that activates KLF4 expression. APTO-253 is currently in phase 1 clinical studies in patients with solid tumors.

The editors of this special section are very grateful to the contributors, whose articles were essential for the development of this highly focused section on KLF4 and cancer. Their insights and important remarks and suggestions will help to accelerate the application of KLF4 as a novel biomarker and its targeting in clinical studies for cancer patients. Clearly, the new designs of KLF4 agents or chemicals that inhibit or activate KLF4 should be developed and tested clinically for potential use clinically—either alone or in combination with existing therapies—in patients who are refractory to conventional therapeutics. The editors acknowledge the assistance of Leah Moyal, Kevin Li, and Ailina Heng for their significant editing and preparation of the material in this section.

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