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COMMENTARY

Role of YY1 in Pathogenesis of Cancer

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I. FACTS

I.A. YY1 Expression in Tumors

Accumulating data indicate a deregulated expression of YY1 in numerous tumor types.[1,2] Following all of the meeting sessions and exploitation of different methodologies, the overexpression of YY1 in tumors was clearly identified.

1. A thorough computational analysis of YY1 gene expression levels highlighted a significant increment of the YY1 transcript in both the examined solid tumors and hematological malignancies, in comparison with their normal counterparts.
2. Immunohistochemical evaluation in combination with a new semiquantitative technology, such as quantum dot labeled immunohistochemistry, documented a significant increase in the expression of YY1 proteins in bone tumors, multiple myeloma, diffuse large B-cell lymphoma, and follicular lymphoma.

I.B. Contribution of YY1 to the Malignant Transformation Process

The putative role of transcription factor YY1 in the pathogenesis of cancer is supported by its known interaction with cell cycle regulation.[1,2] This hypothesis was advocated during the meeting by presentations related to epithelial, mesemchymal, and hematological tumors.

1. In order to determine the risk for lung cancer, the contribution of YY1 was defined by identification of its ability to regulate,

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at the transcriptional level and in opposition to E2F1, the expression of the excision repair cross-complementation group 5 (ERCC5) gene. ERCC5 is an essential enzyme in the nucleotide excision repair of DNA whose dysfunction has already been associated with an increased risk of cancer.[3]

2. YY1 and vascular endothelial growth factor (VEGF) seem to intervene in the pathogenesis of osteosarcoma. In fact, the silencing of YY1 in an osteosarcoma cell line was associated with a decreased VEGF/angiogenesis and a complex rearrangement of the gene expression profile, which resulted in a partial reversion of the malignant phenotype of the cells.[4]

I.C. Identification of Signaling Pathways Associated With YY1

Because of its ubiquitous expression and multifunctional activity, the contribution of YY1 to the development of different tumor types is expected to be related to the cellular and oncotype context.

Data relating to this concept and the application of computational and functional methodologies were presented at the meeting. In addition to a cell cycle perturbation, the presented data implicated a dysregulation in other pathways that are potentially more tissue-specific.

1. The Raf-1 kinase inhibitor protein (RKIP) was reported to antagonize the oncogenic activities of different kinases in MAPK and NF-κβ activation pathways.[5] The reported inversion in the ratio between YY1 and RKIP expression in hepatocellular carcinoma compared with the adjacent nontumoral tissues suggests a direct/indirect regulatory role of YY1 in hepathocyte transformation.
2. The retinoblastoma protein-interacting zinc finger gene RIZ1 is a putative tumor suppressor gene, and RIZ1 inactivation is frequently found in tumors through a loss of mRNA expression.[6,7] In contrast, the overexpression of YY1 in osteosarcoma cells plays a key role in the positive regulation of RIZ1. The co-expression of RIZ1/YY1 proteins suggests a tandem regulatory mechanism in human osteosarcoma cells and tissues.

3. Computational analyses performed with the aim of obtaining information about the potential role of YY1 in NHL indicated a significant association of YY1 gene expression with networks related to cellular movement, cell morphology, cell cycle, carbohydrate metabolism, and cell-to-cell adhesion. Furthermore, in agreement with the physiological roles of this transcription factor, the YY1-associated network with the highest score involved the development of the hematological system and its function.

II. OPEN QUESTIONS

II.A. Quantification of YY1 Protein Level and Definition of Its Subcellular YY1 Location

1. The overexpression of YY1, at both gene expression and protein levels, has been clearly documented in numerous malignancies.[1,2] However, studies aimed at a direct correlation of RNA and protein increase are still limited. Although quantitative methodologies are easily applicable and have been applied to the measurement of YY1 transcript levels, only semiquantitation of the YY1 protein was performed. Studies analyzing these aspects are needed to define the relative significance of YY1 RNA and protein levels as diagnostic and prognostic markers.
2. Although YY1 protein was found to be present both in the nucleus and cytoplasm of tumor cells, a clear relocation after transformation has yet to be documented. The application of biochemical and imaging technologies is needed to define a role of this transcription factor, if any, in the cytoplasm or even on the cell membrane.

II.B. Validation of the Altered Signaling Pathways Associated With YY1

Numerous studies suggest that YY1 plays an important role in a number of biological processes, and accordingly, numerous signaling pathways could be dysregulated as a consequence of YY1 overexpression.[1,6] Molecular and functional analyses are necessary to validate the putative pathways already identified, as well as to clarify whether

some of these pathways are relevant in a tissue-specific context in the transformation process and in tumor progression.

III. IMPLICATIONS AND CONCLUDING REMARKS

Overall, the YY1 implication in the development of different tumor types documented in this session opens the way to its application in selected pathologies, such as lung cancer, as a diagnostic marker for cancer risk and in a wide range of tumors as a prognostic marker. Furthermore, because several studies have indicated that targeted therapies are the new option in the treatment of resistant tumors, the ongoing identification of dysregulated pathways associated with YY1 overexpression, after accurate validation, could greatly contribute to designing new anti-cancer therapeutic tools.

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