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CORR Insights®: MicroRNA Regulates Vascular Endothelial Growth Factor Expression in Chondrosarcoma Cells

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Where Are We Now?

In the last two decades, microRNA (miRNA) has become one of the more promising cancer research areas. Previous research [5] demonstrated the roles of miRNAs in tumor initiation, invasion, angiogenesis,

apoptosis, and metastasis, among other areas. A number of articles [1–9] have investigated miRNAs in sarcomas. Yoshitaka and colleagues [9] evaluated the miRNA expressions in clinical samples from human conventional chondrosarcoma tissue, cell lines, and nontumorous articular chondrocytes. A wide variety of miRNAs were downregulated differently in chondrosarcoma compared to nontumorous articular chondrocytes. The results from the study by Yoshitaka and colleagues [9] showed 27 downregulated miRNAs with only miR-96 and 183 upregulated.

The current study also investigated the relationship between miRNAs and sarcoma. Sun and colleagues [6] concluded that miRNA-181a is a hypoxia-regulated miRNA overexpressed in chondrosarcoma that also enhances VEGF expression. An antagomir-based therapy (antimiRNA-181a) targeted at miRNA-181a may be

effective in blocking angiogenesis and tumor progression in chondrosarcoma. The data focused on hypoxia, VEGF, miRNA-181a, and chondrosarcoma.

Considering the heterogeneous cell population in tumor tissue, is it possible overexpression of miRNA-181a came from other types of cells or just higher proportion of chondrosarcoma cells? This issue must be addressed before reaching a solid conclusion on further applications of miRNA-181a expression in chondrosarcoma.

Where Do We Need To Go?

Previous studies [1, 2, 6, 9] demonstrated that miRNA-181a is neither cell nor tumor specific. Normal chondrocytes, chondrosarcoma, and osteosarcoma have been shown to express miRNA-181a [1, 2, 6, 9]. The current study has made an important contribution in terms of how it demonstrates a pathogenic role for miRNA-181a, particularly in terms of the upregulation of VEGF, and how it may respond to hypoxia in chondrosarcoma cells.

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Still, the roles cannot be defined without more data. In order to obtain these data, we must ask questions like (1) what are the relationships between the miRNAs and other cytokines which upregulate the expression of the VEGF? (2) Can miRNA-181a regulate other angiogenesis growth factors? (3) What are the signaling pathways for micro RNAs for further regulation of VEGF?

In the current study, there is only one chondrosarcoma tissue for Grades II and III, respectively. We would like to know more about the miRNA-181a level in dedifferentiated chondrosarcoma. Researchers must confirm the roles of miRNA-181a in a larger series of tumors, as well as check the correlation between vascularity with VEGF and miRNA-181a in the tissue specimen. The effects of hypoxia and miRNAs seemed more synergistic in an earlier report [9]. If this was indeed the case, then did the effects of hypoxia and miRNA-181a for VEGF overexpression work through different mechanisms or pathways? Further studies are needed to clarify the sources of miRNA-181a and their roles in stressed conditions, as well as in sarcoma behaviors like tumor initiation, invasion, angiogenesis, apoptosis, metastasis, and drug resistance.

How Do We Get There?

Novel approaches to cancer therapy target the suppression of angiogenic

and metastatic pathways. Currently, the efficacy of antagomir-based therapy (antimiRNAs) in sarcomas remains elusive. The potential of miRNA-181a as a biomarker for cancer diagnosis does not seem high because it is not tumor specific. However, the current study provided potential antiangiogenic strategies through an antagomir-based therapy targeted at miRNA-181a.

Despite these potential approaches, there are numerous issues that researchers must first address. Further investigations should (1) clarify the tissue and tumor types specific for miRNA-181a, (2) perform larger-scale studies to confirm this finding, (3) investigate the effect of miRNA-181a on lung metastasis and other clinical parameters, (4) search more target of miR-181a in addition to VEGF, (5) demonstrate the in vivo roles of miRNA-181a in pre-clinical models, (6) develop an effective delivery system of miRNA-181a and antagomir (antimiRNA-181a), (7) compare the effectiveness of antagomirs with other antiangiogenic modalities in pre-clinical models, (8) investigate the biologic effects of additional miRNAs expressed in tumors, and (9) evaluate clinical prognostic parameters like survival of chondrosarcomas, as well as its relationship to miRNAs.

The sarcoma therapy field is just beginning to blossom. As we learn more about miRNA, we must continue

our in vivo investigations and translational researches to determine the various types of pathological roles and therapeutic implications of these molecules. I expect more clinical applications of miRNA to become evident within the next decade.

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