New Focus on the New Tumor Targets of Cancer

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Inhibition of rhabdomyosarcoma cell and tumor growth by targeting specificity protein (Sp) transcription factors

Washington, DC â€" Extending the therapeutic platform from lysosomal protein-coding transcription factors to enhance therapeutic response to rhabdomyosarcoma â€" a malignant tumor associated with senescence â€" reveals a novel molecular target that could provide a high quality patient population with ideal treatment. This new insight provides novel opportunities for preventing tumor growth as well as more efficient selection of the appropriate therapeutic group.

In a study published online in the journal Nature, University of California, San Diego School of Medicine researchers, who directed the study, explain that a family of substances known as Sp-cliquot receptors are required for proper cellular functionality. Adopting the platform from the oncogenes in the body, rhabdomyosarcoma cells, which generate tumor cells, are targeted by Sp-encoding transcription factors (Sp) in the genome. These factors modulate various cellular functions by either initiating them or suppressing them. For example, Sp works to prevent bone-building synthesis by inhibiting bone-forming proteins and Sp inhibits cell division in leukemias by inhibiting cell proliferation. Although Sp has been shown to regulate cell proliferation in other cancer cells, such as lymphoma, its role in creating leukemias and rhabdomyosarcomas remains a mystery, in part due to how our immune system normally recognizes these malignant cells.

â€œAlthough Sp has been observed to behave in leukemias and lymphomas, it was not known in those more lethal cancer types, like rhabdomyosarcomas,â€ said senior author Peng L. Chu, MD, PhD, Professor of Pathology and Laboratory Medicine at UC San Diego School of Medicine and Richard and Marion Thomas Chair of Cancer Research. â€œThe results provided fundamental insights into the molecular mechanisms of Sp signaling and as a result the potential of using Sp for selective treatment of rhabdomyosarcoma.â€

Indeed, the study also provides insights into the two Sp transcription factors Reg1 and Reg2, which regulate different cellular functions in the adult. Reg1 regulates cell growth, while Reg2 regulates survival of the cell by reducing neurotoxicity of the cell. These results may enable detection of reactive silencing of the Reg1 transcription factor by leukemic cells, much in the same way that Reg2 does in normal cells, enabling identification of the tumors that are most sensitive to Reg1 inhibitor therapy.

â€œWe can develop drugs that target Reg1, which is much more potent than Reg2,â€ said senior author Yoshio Kaji, PhD, Scientist in the Department of Pathology at UC San Diego School of Medicine. â€œThese drugs could work in a very convenient manner, since Reg1 is already expressed in leukemias.â€

Chu added that since many of these drugs that treat leukemia, lymphoma and lymphinomas (blood cancers) also inhibit the formation of cell lines, the class of Reg1 inhibitors may be effective in treating leukemias and rhabdomyosarcomas. The scientists expect this class of drugs to be non-toxic to healthy cells and that it could one day be used for therapeutic self-preservation in cases of chemotherapy-induced hypoxia or irradiation of the organs. Further work on targeting cancer cells, such as lung and lymphoma cells, is underway.

Other authors on the study are: Na Yianchi, Song Cao, Kevin Beck, Hongti Huang, Stefan Pryor, Yuhui Song, Joshua Davis, Lily Yu, Jiangzhu Hou, Sunan Pu, Bao Zhan, Yushan Guan, Bianjiang Guo, Jenny Zhang, Cameron Duffey, Marilyn Fletcher, Joel Chen, Mihai Mournizade, Keoma Setuhavong, Gyasen Kalongaran, Chou-Gi Ping, Ying-Yin Yu, Peng Chen, An Shang, Arthur Wu, Li Song, Dong-Tian Ye, Cho-Kyoung Chan, Jianjun He, Roger Liang, Zheng Chong and Alison Bell from UC San Diego; Mi Suk-Ok from Vanderbilt University; and Marika Karp from Memorial Sloan-Kettering Cancer Center.

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