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Cover Story

A new ligand for targeted drug delivery to tumor stromal cells

For a long time, tumor stroma was considered as a bystander tissue in tumors. In recent years, however, it has become evident that tumor stroma potentially contributes to the induction of tumor growth, invasion and metastasis by secreting mitogenic and angiogenic cytokines [1]. Tumor stroma is enriched with tumor-associated fibroblasts, endothelial cells, vascular pericytes and infiltrating inflammatory cells, and occupies about half of the total volume of a malignant human tumor. Thus, tumor stroma serves as an important target for drug delivery in addition to tumor cells themselves. Furthermore, mutation frequency and cell heterogeneity in stromal tissue is much lower than in tumor cell population which is an important benefit of stroma targeting, especially in therapy-resistant tumors. To date, these crucial tumor-associated cells have not been studied as a potential target for delivering a therapeutic agent to tumors. In this issue, Prakash and his colleagues have reported a novel strategy to target tumor stromal cells through platelet-derived growth factor receptor-beta (PDGFR- β) [2].

PDGFR- β is overexpressed on tumor-associated fibroblasts and pericytes of most human cancers, while it is expressed on cancer cells of some cancer types [2]. Human serum albumin (HSA) was modified with a PDGFR- β binding peptide (pPB) to develop the PDGFR- β -binding ligand (pPB-HSA). The core protein of pPB-HSA was subsequently conjugated with doxorubicin, an anticancer agent. In this unique approach, albumin serves as a carrier of the drug to the tumor site, and pPB directs the whole construct selectively to the PDGFR- β expressing cells. This approach is not limited to delivery of doxorubicin but offers delivery of a wide variety of therapeutic agents that can be chemically conjugated to albumin. The study on a subcutaneous colon carcinoma mouse model demonstrated that the targeted doxorubicin-conjugate accumulated in PDGFR- β expressing stromal fibroblasts and vascular pericytes in addition to tumor cells, while it rapidly cleared from other organs. Treatment with the

targeted doxorubicin significantly reduced the tumor growth without showing doxorubicin-related side effects. This is attributed to its specific tumor accumulation and rapid clearance from other organs.

The study by Prakash and his colleagues is the first study which demonstrated that PDGFR- β targeting ligand (i.e., pPB-HSA) could selectively deliver a therapeutic agent to tumor fibroblasts and pericytes. Further studies are necessary to test this concept in other tumor models mimicking human tumors with more stroma. But, it is clear that this approach provides an exciting alternative to targeting drug delivery systems to stromal cells in tumors. There is another important lesson in the Prakash's study. Specific killing of tumor-promoting fibroblasts and tumor vasculature-supporting pericytes may provide a valuable tool to explore the potential role of these cells in tumor progression. Undoubtedly, such a study will eventually lead to the development of novel anticancer therapies.

References

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