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DPAGT1 Inhibitors: Discovery of Anti-Metastatic Drugs

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Abstract : Alterations in glycosylation not only directly impact cell growth and survival but also facilitate tumor-induced immunomodulation and eventual metastasis. Identification of cell type-specific glycoconjugates (tumor markers) has led to the discovery of new assay systems for certain cancers via immunodetection reagents. N- and O-linked glycans are the most abundant forms of glycoproteins. Recent studies of cancer immunotherapy are based on the immunogenicity of truncated O-glycan chains (e.g., Tn, sTn, T, and sLea/x). The prevalence of N-linked glycan changes in the development of tumor cells is known; however, therapeutic antibodies against N-glycans have not yet been developed. This is due to the lack of specificity of N-linked glycans between normal/healthy and cancer cells. Abnormal branching of N-linked glycans has been observed, particularly in solid cancer cells. While the discovery of drug-like glycosyltransferase inhibitors that block the biosynthesis of specific branching has a very low likelihood of success, altered glycosylation levels can be exploited by suppressing N-glycan biosynthesis through the inhibition of dolichyl-phosphate N-acetylglucosaminephosphotransferase1 (DPAGT1) activity. Inhibition of DPAGT1 function leads to changes of O-glycosylation on proteins associated with mitochondria and zinc finger binding proteins (indirect effects). On the basis of dynamic crosstalk between DPAGT1 and Snail/Slung/ZEB1 (a family of transcription factors that promote the repression of the adhesion molecules), we have developed pharmacologically acceptable selective DPAGT1 inhibitors. Tunicamycin kills a wide range of cancer and healthy cells in a non-selective manner. In sharp contrast, our DPAGT1 inhibitors display strong cytostatic effects against 16 solid cancers, which require the overexpression of DPAGT1 in their progression but do not affect the cell viability of healthy cells. The identified DPAGT1 inhibitors possess impressive anti-metastatic ability in various solid cancer cell lines and induce their mitochondrial structural changes, resulting in apoptosis. A prototype DPAGT1 inhibitor, APPB has already been proven to shrink solid tumors (e.g., pancreatic cancers, triple-negative breast cancers) in vivo while suppressing metastases and has strong synergistic effects when combined with current cytotoxic drugs (e.g., paclitaxel). At this conference, our discovery of selective DPAGT1 inhibitors with drug-like properties and proof-of-pharmaceutical concept studies of a novel DPAGT1 inhibitor are presented.

Keywords : DPAGT1 inhibitors, anti-metastatic drugs, natural product based drug designs, cytostatic effects
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