Compositions and methods related to the expression of Globo H and SSEA3 in breat cancer stem cells

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摘要

Cancer stem cells (CSCs) possess the capability of stem cells to multiply and differentiate into their progenitors, display resistance to chemotherapy and radiation therapy, and could be the root cause for relapse and metastasis of cancerous tumors. Hexasaccharide Globo H is overexpressed in many epithelial cancers and has been used as a vehicle in developing an immunotherapeutic vaccine for breast cancer. Gb5 is a pentasaccharide precursor of Globo H, also known as "SSEA". Gb5 has been known as a marker for human embryonic stem cells that can be spotted only in stem cell labs during the embryonic developing stages. We examined the expression in breast cancer stem cells (BCSCs) of Globo H. Flow cytometric analysis of 31 human breast cancer specimens revealed that 19 tumors (61.3%) expressed Globo H. Non-BCSCs from all 19 tumors and BCSCs from 6 of 30 (25%) expressed Globo H. We also demonstrated for the first time the expression of stage specific embryonic antigen 3 (SSEA3), the pentose precursor of Globo H, in 14 of 18 (77.8%) breast cancer and 10/18 (55.6%) BCSCs. SSEA3 was detected in non-BCSCs from all 14 SSEA3-expressing tumors. Similar to Globo H, SSEA3 expression on normal cells is essentially restricted to apical epithelial cells at lumen borders, a site that appears to be inaccessible to the immune system. Immunization of mice with Globo H-KLH conjugate induced antibody reactive with not only Globo H but also SSEA3, suggesting that Globo H-based immunotherapy will target not only non-BCSCs but also BCSCs. We next sought to reduce Globo H expression by siRNA targeting fucosyltransferase (FUT) 1 and 2, which are responsible for alpha-1, 2 linkage of fucose. We showed for the first time that both genes were involved in the biosynthesis of Globo H. Moreover, FUT2 expression in BCSCs was significantly lower than non-BCSCs harvested from a xenografted primary human breast cancer in NOD/SCID mouse, while FUT1 was slightly lower in BCSCs. Thus, the lower expression of Globo H in BCSCs may be attributed in part to lower levels of FUT2/FUT1, and in part to the less frequent expression of SSEA3 in BCSCs than non-BCSCs. The invention provide new insight into further development of Globo H-based vaccine and FUT1/FUT2 targeted therapy for breast cancer.

技術優勢

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應用範圍

Development of Globo H-based vaccine and FUT1/FUT2 targeted therapy for breast cancer.

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