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Grant Title: A mechanism for evasion of CTL immunity by tumors expressing core2 *O*-glycans

Abstract

Purpose: Our tumor immunosurveillance system has an ability to reject tumors, thereby limiting cancer progression and metastasis. In the tumor rejection system, two major effector lymphocytes, natural killer (NK) cell and cytotoxic T lymphocyte (CTL) play a critical role. However, the metastatic spread is still the major cause of cancer deaths despite the effector function of these lymphocytes, since metastatic cancer cells acquire an ability to evade the tumor rejection response by NK cell and CTL. We previously reported the novel immune evasion mechanisms from NK killing by cancer cells expressing a certain type of branched *O*-glycan called core2 *O*-glycan (*1, 2*). The results from recent pathological survey suggested that the cancer cells expressing core2 *O*-glycan also evade CTL killing. Our goal is to understand the immune evasion mechanism from CTL immunity by cancer cells expressing core2 *O*-glycan.

Methods: Core2 β-1,6-*N*-acetylglucosaminyltransferase (C2GnT) is responsible for the synthesis of core2 *O*-glycan. To examine the *O*-glycosylation status, we prepared C2GnT-expressing cancer cells to analyze the *O*-glycosylation of the cell-surface molecules biochemically. Tumor rejection system by CTL includes the multiple steps. To identify which step is impaired by cancer cells expressing core2 *O*-glycan and to understand the molecular mechanism of immune evasion from CTL killing, we established the tumor antigen-specific CTL clones to make a comparison of susceptibility to CTL attack between C2GnT-non-expressing and C2GnT-expressing cancer cells.

Results: The results we have obtained over past two years were:

- The expression of C2GnT resulted in the modification of cell-surface molecules with core2 *O*-glycans containing poly-*N*-acetyllactosamine (*3*).
- Core2 *O*-glycans had no influence on the presentation of the tumor peptide by dendritic cells.
- Major histocompatibility class I molecule (MHC I) was modified with core2 *O*-glycans in C2GnT-expressing bladder cancer cells.
- C2GnT-expressing bladder cancer cells evaded CTL killing *in vitro* (Fig. 1).

These results strongly suggest that the step for the recognition of the tumor antigen peptide-MHC I complex by CTL is impaired in C2GnT-expressing cancer cells. In the near future, we will unveil the detailed molecular mechanisms underlying the impaired peptide recognition by CTL.

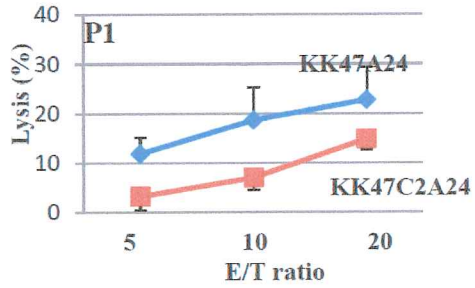

Fig. 1 Immunoevasion from CTL killing by C2GnT-expressing cancer cells
KK47A24, bladder cancer cells (KK47) expressing HLA-A24; KK47C2A24, KK47A24 cells expressing C2GnT. P1, A peptide derived from a tumor antigen, MAGE-3. Target cancer cell lysis by P1-specific CTL was measured. E/T, effector / target.

References

1. S. Tsuboi *et al.*, *EMBO J* **30**, 3173 (2011). 2. Y. Suzuki *et al.*, *Int J Oncol* **40**, 1831 (Jun, 2012).
3. T. Okamoto *et al.*, *Mol Med Rep* **7**, 359 (Feb, 2013).