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Natural antibodies identified as potential anti-tumor agents

Shumpei Ishikawa Professor of Genomic Pathology at TMDU

Q Your focus is on B-cell immunity in cancer. Please give us a brief overview of your latest findings

A: I have been working with my TMDU colleagues to clarify the architecture of B-cell immunity in cancers. B cells, together with Tcells, are subsets of lymphocytes within the immune system. There is substantial evidence that these cells play a pivotal role in the immune system's fight against cancers, although B-cell activity remains relatively elusive compared to the well-studied T-cell system.

In our study in *Cell Reports*, we initially investigated the global landscape of anti-tumor immunity through an "immunogenetics" approach where antigen receptor repertoires of B and T cells were clarified by next-generation sequencing. We found: (1) highly clonal infiltration of B cells in cancer tissues; (2) prominent IgG-type B cells in tumor tissues; and, (3) substantially different profiles of B-cell repertoire between individuals. We then paid closer attention to the dominant B-cell clones in each cancer case, and artificially reconstructed the highly clonal immunoglobulins, or antibodies (Abs). By identifying tumor-antigens that correspond to those Abs, we found that, although a portion of B-cell immunity is shaped by abundant cellular auto-antigens, a substantial portion of tumor-resident B cells produce functional Abs. In particular, we identified anti-sulfated glycosaminoglycans (sulfated-GAGs) Abs, which showed robust growth-suppression against gastric cancer cells and a wide variety of other human malignancies. HSGAG (heparan sulfate glycosaminoglycan) is a common type of sulfated GAGs found on cell surface, and its tumor-specific structures and functions are also hypothesized to date.

Q What made you focus on gastric carcinoma and B Cells?

A: Gastric carcinoma (GC) is one of the most frequent malignancies worldwide. Diffuse-type gastric carcinoma (DGC), which accounts for more than 30% of GCs, shows the worst prognosis among gastric tumors. Although we have identified several frequent genetic mutations in DGCs, including RHOA, targeted therapies against such classically non-druggable proteins have not yet been established. Anti-tumor immunotherapy has gained considerable attention recently and GCs might also be good candidates for it. Through an integrative analysis of The Cancer Genome Atlas (TCGA) database, we found higher B-cell infiltration specifically in DGC cases compared to other types of GCs; thus, we were motivated to study precise B-cell immunity in cancers by focusing on DGCs.

Q How does your research align with the focus areas of TMDU?

A: At TMDU, there is a strong focus on cancer research and well-established facilities for supporting translational research. One of TMDU's goals is to expedite the discovery of new diagnostic tools and treatments to contribute to society and humanity.

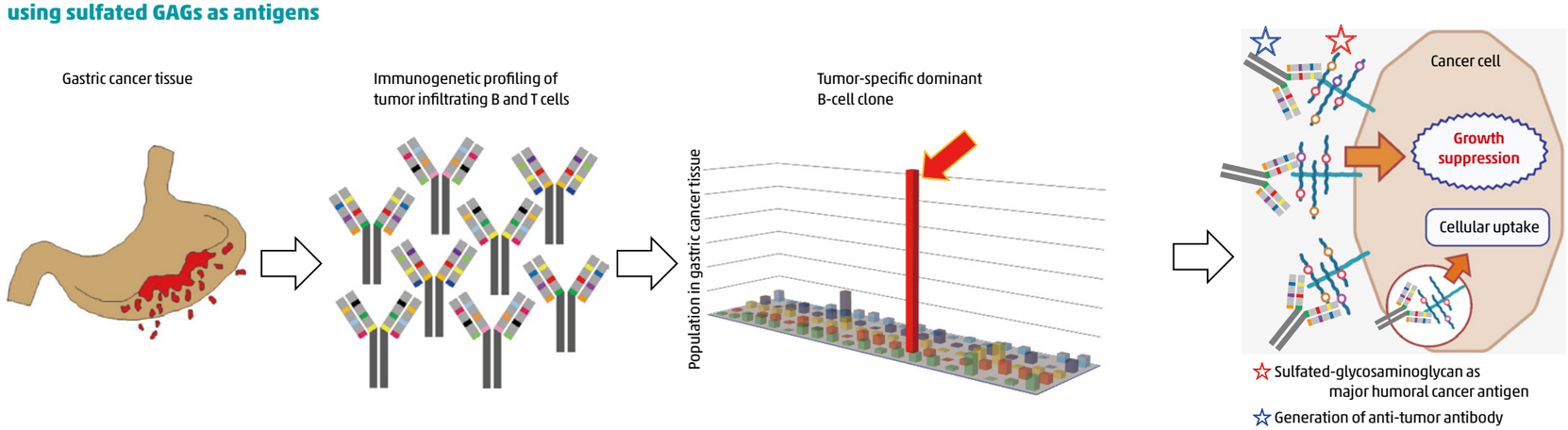
Q What are the future directions and challenges of your research?

A: Although the Abs identified in our study exerted growth-suppressive effects against a wide variety of human malignancies *in vitro*, their molecular functions and behaviors *in vivo* are still open questions. Identification of more specific structures of the HSGAG antigens is one of the most important aims of future research to clarify the precise function and safety of the Abs we identified. Also, it is important to perform in-depth evaluation of the safety and efficacy of the anti-HSGAG Abs in *in vivo* models.

Q What are the clinical implications of your study?

A: One of the most important points of our study is that we identified HSGAGs as the major and functional B-cell antigen in cancer environments. Our findings shed light on the immunologic aspects of HSGAGs and might encourage clinical communities to develop HSGAGs such as heparin as a cancer vaccine. From an optimistic point of view, combined therapies with a state-of-the-art anti-PD-1 immune stimulant and patient stratification based on pre-existing anti-HSGAGs immunity would maximize the efficacies and benefits of the heparin as a cancer vaccine. Going forward, the adoption of more extensive profiling of tumor-infiltrating B cells is expected to pave the way toward understanding tumor immunity, and to help discover tumor antigens and natural anti-tumor Abs to fight against refractory cancers.

Identification of tumor-specific dominant B cells, and immunotherapy using sulfated GAGs as antigens



Dr. Ishikawa graduated from the Faculty of Medicine at the University of Tokyo in 2000 and received his PhD in Pathology. He performed postdoctoral research in the Genome Science Division of the Research Center for Advanced Science and Technology at the University of Tokyo. He became Associate Professor in the Department of Pathology there, and joined TMDU as Professor of Genomic Pathology in 2013.

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A new graduate program on preemptive and precision medicine launched at TMDU

Hajime Karasuyama
Executive Director / Executive Vice President

TMDU will launch a new graduate program called "Integrative Sciences for Preemptive Medicine" in April 2018.

The new program will offer an innovative academic framework for providing preemptive and precision medicine. In addition to using traditional methods of gathering, managing, and analyzing data from individual genetic or epigenetic profiles and electronic clinical records, researchers will also utilize IoT, ICT, and AI technologies. Using all of these methods, they can gather, manage, and analyze real-time information on an individual's lifestyle and relevant environmental factors in an integrated manner.

It is increasingly clear that researchers today must be able to analyze medical big data in an integrated fashion in order to achieve higher accuracy in preemptive and precision medicine. To that end, this new program will offer critical opportunities to learn about preemptive and precision medicine to interested students of all academic backgrounds – whether medicine, dentistry, or engineering science. Such an approach will bring together faculty and students from diverse academic backgrounds. Through their collaboration, they will be able to discover novel findings heretofore unknown in medical research, and thus create a predictive system that promises to optimize medicine and health.

At a time when death from infectious disease has decreased, yet the number of patients with lifestyle-related diseases is on the rise, we are determined to train healthcare professionals to conduct preemptive and precision medicine capable of predicting disease at the individual level and delivering optimized therapies for each patient.