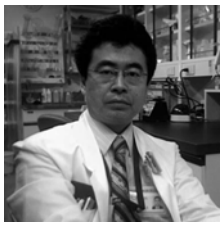

Title of Project : Scientific research of transplantation tolerance targeting CD26/caveolin-1 costimulation pathway

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Research Area : Medicine, dentistry, and pharmacy

Keyword : Pediatric hematology

【Purpose and Background of the Research】

CD26 is a 110 kDa surface glycoprotein, and its role in immune regulation has been extensively characterized, with recent findings elucidating its linkage with signaling pathways and structures involved in T cell activation as well as antigen presenting cell (APC)-T cell interaction, which has been demonstrated to be exerted via CD26-caveolin-1 interaction.

Graft-versus-host disease (GVHD) remains a major cause of morbidity and mortality in allogeneic stem cell transplantation (alloSCT). In GVHD, mature donor T cells that accompany the stem cell graft attack recipient tissues, especially the skin, liver, gastrointestinal tract, and lung. Therefore, all patients undergoing alloSCT receive GVHD prophylaxis to impair T cell function; however, treatment to prevent GVHD can be deleterious since mature donor T cells play a critical role in mediating reconstitution of the adaptive immune system, especially in adults with diminished thymic function. Recipients of alloSCT are thus at great risk for infections, particularly when prolonged immunosuppressant is required for treatment of GVHD. Therefore, we attempt to establish therapeutic innovations by approaches that aim to minimize GVHD by targeting CD26-mediated T cell regulation.

【Research Methods】

Using hu-PBL-SCID mice, in which human peripheral lymphocytes are functioned as effector cells for xenogeneic GVHD (x-GVHD), the studies will be conducted on functional analyses of human T cell CD26 in GVHD, and on transplantation tolerance targeting CD26/ caveolin-1 costimulation pathway;

[1] Analysis of CD26-mediated T cell costimulation pathway triggered by caveolin-1.
[2] Development of specific T cell suppression therapy targeting CD26/caveolin-1 interaction.
[3] Molecular analysis of CD26/caveolin-1 interaction on transplantation tolerance.

【Expected Research Achievements and Scientific Significance】

Influencing CD26 mediated T cell costimulation by using caveolin-1-Fc fusion proteins or by inhibiting dimerization with selected small compounds may lead to new therapeutic approaches to treat T_H1-mediated autoimmune diseases such as rheumatoid arthritis, Grave's disease and multiple sclerosis, and alloreaction following transplantation or atherosclerosis, and to induce adjuvant reaction for T_H1 mediated cancer immunotherapy.

Of significance is our recent work demonstrating that CD26 on T cell surface binds to caveolin-1, hence identifying the first endogenously expressed CD26 costimulatory ligand in the immune system.

Moreover, the caveolin-1-CD26 interaction results in strong T cell costimulation as a result of the recruitment of a molecular complex consisting of CARMA1 in lipid rafts. Our findings will therefore serve as a foundation for future insights into the regulation of T cell costimulation via the CD26 molecule, leading to be possible that the novel therapeutic approach to minimize GVHD will be realized by targeting CD26-mediated T cell regulation.

【Publications Relevant to the Project】

・Ohnuma K, Dang NH, Morimoto C. Revisiting an old acquaintance: CD26 and its molecular mechanisms in T cell function. *Trends Immunol.* 2008;29:295-301.

・Ohnuma K, Uchiyama M, *et al.* Caveolin-1 triggers T-cell activation via CD26 in association with CARMA1. *J Biol Chem.* 2007;282:10117-31.

【Term of Project】 FY2009-2013

【Budget Allocation】 49,500 Thousand Yen

【 Homepage Address and Other Contact Information】

http://www.ims.u-tokyo.ac.jp/cimmuno/index.html