1036 TREG-SPECIFIC TCR SIGNALING AS A TARGET OF CANCER IMMUNOTHERAPY

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Background Regulatory T (Treg) cells are essential for suppressing immune responses against self-antigens to prevent autoimmunity and maintain immune homeostasis. However, Treg cells highly infiltrate into various tumor tissues and also suppress effective anti-tumor immune responses. Indeed, high infiltrations of Treg cells correlate with poor prognosis in various tumors and removal of Treg cells is able to evoke and enhance anti-tumor immunity. For this reason, new cancer immunotherapies targeting Treg cells are being developed, yet systemic depletion of Treg cells may concurrently elicit autoimmunity. Thus, how to specifically target and deplete Treg cells for augmenting anti-tumor immunity while evading autoimmunity *in vivo* is important for its therapeutic application. Treg and conventional T (Tconv) cells differ in TCR signaling at basal state and upon TCR stimulation due to Treg-specific downregulation of certain TCR signaling molecules, including Lck and ZAP-70 tyrosine kinases. Since these kinases are essential for sustaining Treg and Tconv cells, Treg-specific regulation mechanism makes Lck a suitable target for selective control of Treg cells.

Methods Small molecules with Lck inhibition activity were assessed in mice and humans for selective depletion of Treg cells and activity of $CD8^+$ T cells *in vitro* or *in vivo* in tumor-bearing mouse models.

Results Orally-available small molecule with Lck specific inhibition activity effectively reduced Ki-67^+ effector Treg cells *in vitro* and *in vivo* in a dose-dependent manner. This reduction in effector Treg cells conversely expanded tumor-specific $CD8^+$ T cells and effectively reduced tumor growth in mice without autoimmune side-effects. Similarly, imatinib, a tyrosine kinase inhibitor for oncogenic BCR-ABL fusion kinase with off-target effects on Lck, was found to preferentially deplete effector Treg cells and allowed expansion of antigen-specific $CD8^+$ T cells in healthy individuals and in mice.

Conclusions The results suggest that TCR signaling molecules under Treg-specific regulation can be a potent mechanistic target for selectively controlling Treg cells to augment anti-tumor immunity.

Ethics Approval All studies involving animals and human samples were carried out in accordance with the protocols approved by the institutional ethics committee of Osaka University.

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