

T-Cell Responses to Cyclin B1 Are Not Restricted to p53-Overexpressing Tumors

To the Editors: In their elegant study, Sorensen et al. showed the existence of a T-cell response to two cyclin B1-derived peptides in patients with advanced-stage breast cancer, confirming initial observations by Kao that cyclin B1 is an interesting target for immunotherapy (1, 2). However, the authors reported the absence of cyclin B1-specific T cells in 10 of 10 healthy donors and concluded that they are only present after tumor-driven immune activation in patients with p53/cyclin B1-overexpressing tumors.

This is in contrast to our findings (3).¹ We have characterized the cyclin B1 peptides 44(ALGDIGNKV), 204(ILIDWLQV), and 218(LLQETMYMT) as immunogenic HLA-A*0201-binding amino acid sequences. Antigen-specific T cells were detected in five of six T-cell cultures in all of three healthy donors without the need for a heteroclitic modification.

How can this discrepancy be explained? The authors used a single stimulation with peptide-pulsed peripheral blood mononuclear cells. In our experience, repetitive use of purified, professional antigen-presenting cells is more efficient in expanding antigen-specific T cells. We therefore used an efficient expansion system based on CD40-activated B cells to identify cyclin B1 epitopes (3). Furthermore, the culture with high amounts of peptide (10 μ mol) in combination with nonprofessional antigen-presenting cells potentially promotes the expansion of low-avidity T cells, which would be peptide specific but not tumor reactive (4, 5). Taken together, the different results can be explained by the methodology alone.

Nevertheless, it could be linked to the different epitope classes: peptides abundantly presented by MHC and thus efficiently elutable versus peptides identified by reverse immunology translating to differential thymic expression and deletion. However, for other cyclin family members, the absence of T cells in healthy donors had previously been suggested but seems to depend on the T-cell expansion system used (6), a major challenge in tumor antigen discovery (7).

Our findings suggest that cyclin B1-specific T cells are readily expandable in healthy individuals even if potentially at a lower frequency. For a tumor antigen, this is important. Why? First, cyclin B1 is overexpressed in several hematologic malignancies and thus could be targeted using *ex vivo* or *in vivo* expanded donor T cells in the context of allogeneic stem cell transplantation. Second, p53 mutation and thus cyclin B1 expression are events that occur early in tumorigenesis and are essential to tumor survival. Cyclin B1 is overexpressed in several major tumors. Thus, it has the hallmarks of an antigen for preventive cancer vaccination. If proven safe in advanced can-

cer patients, induction of a prophylactic cyclin B1-directed T-cell response would be an intriguing strategy at least in high-risk cancer families.

Michael S. von Bergwelt-Baildon
Alexander Shimabukuro-Vornhagen
Laboratory for Tumor and
Transplantation Immunology and
Stem Cell Transplantation Program
Department I of Internal Medicine
University Hospital of Cologne
Cologne, Germany

Nela Klein-Gonzalez
Laboratory for Tumor and
Transplantation Immunology
Department I of Internal Medicine
University Hospital of Cologne
Cologne, Germany

Eisei Kondo
Department of Hematology and Oncology
Okayama University Hospital
Okayama, Japan

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References

1. Sørensen RB, Andersen RS, Svane IM, et al. CD8 T-cell responses against cyclin B1 in breast cancer patients with tumors overexpressing p53. *Clin Cancer Res* 2009;15:1543-9, Epub 2009 Feb 17.
2. Kao H, Marto JA, Hoffmann TK, et al. Identification of cyclin B1 as a shared human epithelial tumor-associated antigen recognized by T cells. *J Exp Med* 2001;194:1313-24.
3. Kondo E, Gryschock L, Schultze JL, von Bergwelt-Baildon MS. Using CD40-activated B cells to efficiently identify epitopes of tumor antigens. *J Immunother* 2009;32:157-60.
4. Kroger CJ, Amoah S, Alexander-Miller MA. Cutting edge: dendritic cells prime a high avidity CTL response independent of the level of presented antigen. *J Immunol* 2008;180:5784-8.
5. Kondo E, Maecker B, Draube A, et al. The shared tumor associated antigen cyclin-A2 is recognized by high-avidity T-cells. *Int J Cancer* 2009;125:2474-8.
6. Kondo E, Maecker B, Weihrauch MR, et al. Cyclin D1-specific cytotoxic T lymphocytes are present in the repertoire of cancer patients: implications for cancer immunotherapy. *Clin Cancer Res* 2008;14:6574-9.
7. Kessler JH, Melief CJ. Identification of T-cell epitopes for cancer immunotherapy. *Leukemia* 2007;21:1859-74.

Published OnlineFirst 11/10/09.
© 2009 American Association for Cancer Research.
doi:10.1158/1078-0432.CCR-09-1640

¹ M.S. von Bergwelt-Baildon, unpublished results.