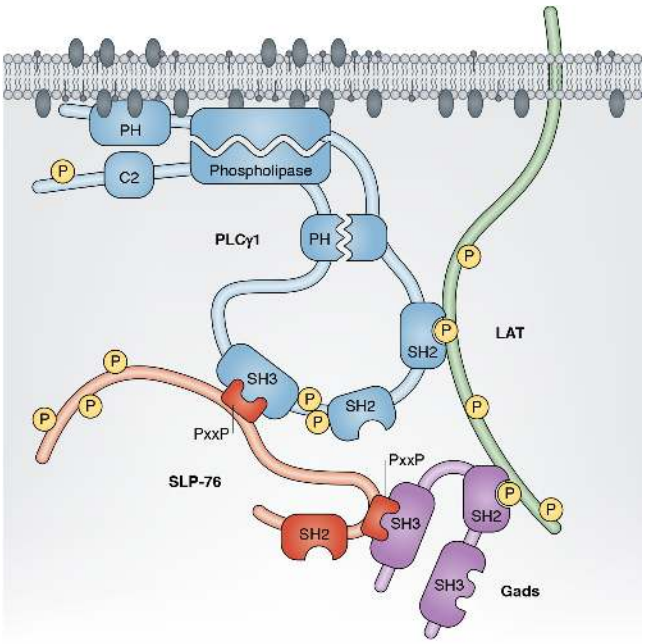
Human LAT mutation results in immune deficiency and autoimmunity but also raises questions about signaling pathways

Insight from Arthur Weiss

TCR signaling, necessary for normal T cell development and T cell function, proceeds through the induction of protein phosphorylation of downstream molecules, including the membrane-anchored adaptor LAT. LAT, a substrate of the ZAP70 tyrosine kinase, is phosphorylated on multiple tyrosines that serve as docking sites for the recruitment of several effector molecules, including PLCγ1, Gads/SLP-76, and Grb2/SOS, that are responsible for induced increase in Ca^{2+} and activation of the Ras/MAPK pathway.

Human immune deficiencies often reveal unexpected functions or highlight differences between human and mouse immune systems. In this issue, Keller et al. describe a family with three children that are homozygous for LAT mutations leading to premature LAT truncation, eliminating all of its known tyrosine phosphorylation sites. The clinical phenotypes of these patients were heterogeneous, characterized by aspects of immune deficiency and autoimmunity. Most noteworthy, some T cells developed in these patients. Interestingly, stimulation of the TCR on the T cells of the one patient that could be studied resulted in a substantial calcium increase and evidence of NF-κB activation but no Erk activation.



The development of some T cells in these patients is surprising, as are the signaling studies. Germline deletion of LAT in mice results in profound early thymocyte developmental arrest, resulting in complete absence of peripheral T cells. It is possible that some LAT-related molecule might compensate for the loss of LAT function in the human, but efforts to identify such molecules were not productive. Alternatively, the truncated LAT protein might not represent a complete loss-of-function mutant. However, the authors examined the function of the truncated mutant in a LAT-deficient Jurkat T cell where they confirmed that the mutant LAT molecule did not support PLCγ1 phosphorylation, Ca^{2+} increase, Erk phosphorylation, or CD69 induction. Thus, the authors' findings with the mutant LAT provided the expected phenotype based on previous studies with LAT mutants in Jurkat and in mice.

So what accounts for the preserved signaling and somewhat preserved T cell development in the patient cells? There is no clear explanation. The mouse and Jurkat systems may differ from signaling systems in human T cells. Most puzzling, however, is the observation that increases in Ca^{2+} and Erk, which are usually coupled and downstream of PLCγ1 activity, are discordant here. These studies would suggest a pathway leading to calcium increase that is dissociated from the activation of PLCγ1 operates in human but not in mouse or Jurkat T cells. These studies present an interesting and puzzling set of observations that await explanation.

Keller, B., et al. 2016. *J. Exp. Med.* http://dx.doi.org/10.1084/jem.20151110

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Combination immunotherapy for cancer

Insight from Douglas Fearon

In this issue, Chapuis et al. describe the response of a single patient with metastatic melanoma to combination immunotherapy with anti-CTLA4 and adoptive T cell therapy (1). Although *JEM* usually discourages the submission of single case studies, the editors, like the authors, realized that this patient was unusual. He had previously been treated with anti-CTLA4 and adoptive T cell therapy administered as monotherapies, with only possible slowing of tumor growth with the former, and no response to the latter. The subsequent complete and durable clinical response to simultaneous treatment with these two modalities, therefore, allowed an argument to be made that their combination was responsible for the improved outcome.

The efficacy of blocking antibodies to CTLA4, PD1, PD-L1, and adoptive T cell therapy, including CAR T cells, has been established, but only a minority of patients with certain cancers respond. The challenge now is to increase both the proportion of patients and the types of cancers that respond to immunological interventions. The finding by Chapuis et al., when taken together with an earlier demonstration of the clinical benefit of combining anti-CTLA4 and anti-PD1 in patients with melanoma (2), argues that combining interventions that target different components of an anticancer immune response may be a feasible strategy. The question is, how will the most therapeutically effective combinations be determined?

Chapuis et al. combined adoptive T cell therapy with anti-CTLA4 because "an ex vivo source of melanoma-reactive CTL might not only provide sufficient substrate for anti-CTLA4 to enhance tumor lysis, but also trigger the development of de novo responses to nontargeted antigens." Postow et al. (2) combined anti-CTLA4 and anti-PD1 because "in preclinical models, combined blockade of PD-1 and CTLA-4 achieved more pronounced antitumor activity than blockade of either pathway alone." These clinical experiments were based on preclinical experimental work, as is appropriate. How might this rationally scientific pathway be enhanced?

The Chapuis et al. study also addresses this issue. Instead of being funded by the pharmaceutical industry, financial support was derived from the government and SU2C, a charitable program of the Entertainment Industry Foundation. This may become the model for cancer immunotherapy. There has been remarkable philanthropic support for this field, as exemplified not only by SU2C, but also by the recent gifts from Michael Bloomberg, Sidney Kimmel, and Sean Parker to establish cancer immunology centers at several academic institutions. This development will allow clinical investigators to focus only on science when developing strategies for combination immunotherapies.

1. Chapuis, A.G., et al. 2016. *J. Exp. Med*. http://dx.doi.org/10.1084/jem.20152021

2. Postow, M.A., et al. 2015. *N. Engl. J. Med*. 372:2006–2017.

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