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From pipe dream to donor-specific PC elimination: Novel ways to target alloantibodies

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A more accurate assessment has identified pretransplant and de novo donor-specific antibodies (DSA) as critical barriers to successful solid organ transplantation. A recent study of patients waitlisted for renal transplantation reported that almost 50% had been sensitized with approximately 6% having panel reactive antibodies of >98%¹. De novo DSA can develop posttransplantation, and both preformed and de novo DSA can mediate acute and chronic antibody mediated rejection². Previous transplantation and pregnancy accounted for >75% of all sensitizing events, and the consequences of sensitization include an increase in median waiting and a higher risk for graft loss.

Sustained increases in DSAs can be linked to a prolonged output of short-lived plasma cells (SLPC) by germinal centers, a continuous differentiation of memory B cells into SLPC by germinal center-dependent and -independent processes, and long-lived plasma cells (LLPC) surviving primarily in bone marrow niches. Immunosuppression that targets the CD28-B7 and CD154-CD40 interactions have recently been shown to abrogate established germinal center B cell responses, and the differentiation of memory B cells into SLPC^{3,4}. However, eliminating LLPC has proven to be challenging. Bortezomib, an inhibitor of the 26S proteasome subunit, can deplete SLPC and LLPC⁵, but continuous dosing is necessary to overcome replenishment of the PC compartment. Thus, drug-related toxicities, as well as the potential for a permanent loss of LLPCs responsible for protective humoral immunity, limit the widespread use of bortezomib. There is therefore a need for new ways to more selectively target LLPC that are responsible for DSA production.

Two recent publications provide tantalizing support for the possibility that selective depletion of LLPC producing DSA could be achieved, while sparing PC producing viral specific antibodies. Halliley and co-workers⁶ provided insights with their work published in *Immunity* into why serum antibodies responding to measles and mumps have a varying half-lives with some surviving >100 years. The authors reported on the heterogeneity of LLPC in human bone marrow and showed that CD20⁻ LLPC distinguish 4 CD38⁺ PC subsets, based on their expression of CD19 and CD138. CD19⁺ PCs were the most recently generated, and had a higher expression of surface Ig, HLA-DR and Ki-67, a marker of recent cell

proliferation. Specifically, these markers were most prominent in the CD19⁺CD38⁺CD138⁻ subset, and gradually declined with PC maturation. The CD19⁻CD38^{hi}CD138⁺ subset was the most mature, did not express surface Ig, HLA-DR or Ki-67, but interestingly, expressed CD28. Furthermore, PCs specific for viruses encountered 40 years earlier, as a result of mumps or measles infection, or tetanus vaccination, were exclusively contained within the CD19⁻CD38^{hi}CD138⁺ subset, whereas PCs specific for influenza were found in the CD19⁺ and CD19⁻CD38^{hi}CD138⁺ subsets. Finally, high-throughput sequence analysis and microscopic analysis pointed towards active lysosomal autophagy as a critical process for LLPC longevity. These findings are relevant to transplantation in 2 ways; firstly, that CD19⁻CD38^{hi}CD138⁺ subset expressing CD28 raise the possibility that belatacept and anti-CD28 antagonists might be effective at eliminating these cells. Indeed, Lee and colleagues reported that CD28 on bone marrow resident PCs promoted their survival and sustained antibody responses in mice⁷. Second, different modes of allosensitization may generate plasma cells with different longevity, and DSA with different persistence. For instance, DSA generated following blood transfusions tend to be transient, while those produced following rejection are more persistent¹. Thus desensitization protocols may improve if tailored to the modes of sensitization.

In a more recent publication in *Immunity*, Lam and co-workers⁸ characterized a potential vulnerability of LLPC compared to SLPC, wherein the enhanced survival capacity of LLPC was dependent on a higher rate of glucose import that was mediated, at least in part, via an increased expression of the glucose transporter, Glut1. LLPC primarily utilized glucose to glycosylate antibodies, but also for sustaining LLPC through glycolysis and pyruvate generation. Increased pyruvate generation coupled with a superior capacity for pyruvate import into the mitochondria may account for the higher basal oxygen consumption observed in human and mouse LLPC compared to SLPC. Pyruvate import into the mitochondria of LLPC was mediated by the essential pyruvate carriers, Mpc1 and Mpc2. Moreover, induced deletion of Mpc2 in mice resulted in a reduction of LLPC but not SLPC numbers with a more rapid waning of antigen-specific antibody responses and antibody secreting cells. Observations of different metabolic requirements in plasma cell subsets mirror recent reports that differentiating T cells change their metabolic programming to enable distinct effector function⁹. The findings by Lam et al also imply that novel desensitization protocols may be developed based on inhibiting glucose uptake and metabolism. In support, Lee et al¹⁰ reported that a combination of the glycolytic inhibitor 2-deoxyglucose (2-DG), the anti-type II diabetes drug metformin, and the inhibitor of glutamine metabolism, 6-diaso-5-oxo-L-norleucine (DON) prevented or delayed the rejection of fully-mismatched skin and heart allografts in mice. It is tempting to speculate that this regimen may also affect the maintenance of LLPCs.

Clearly we have a long way to go before we are able to specifically target the selective elimination of LLPC producing donor-specific alloantibodies. However, these recent basic science findings provide new hope that such a goal may not be a pipe dream after all. By virtue of the preferential dependence of LLPC survival on autophagy, glucose uptake and mitochondrial pyruvate import, a roadmap for their elimination may now be charted.

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