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Modified antibody in fetal alloimmunization

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In this issue of Blood, Ghevaert et al propose to develop a therapeutic antibody for fetal and neonatal alloimmune thrombocytopenia (FNAIT) that would block the actual antibody in sensitized mothers from binding and therefore prevent, or at least ameliorate, fetal and neonatal thrombocytopenia in fetuses who would otherwise be affected.1 The goal of the group is to engineer an antibody reagent that would on the one hand not engage conventional activating Fc receptors and on the other hand interact normally with FcRn, allowing transplacental passage.

What is the overall problem being dealt with here? It is recognized that FNAIT is caused by a mother becoming sensitized to a platelet antigen expressed on fetal platelets inherited from the father.2 The immunoglobulin G antibodies she produces against this incompatible antigen will cross the placenta and create fetal problems (thrombocytopenia). It is also known that a subsequent affected fetus of the same mother will almost always be more severely affected than the previous fetus.3 Screening for mothers at risk for such sensitization, similar to that used to detect Rh-negative women who are at risk for having fetuses affected with hemolytic disease of the fetus and newborn, has been instituted previously in Norway and other countries as a trial.4 Other than in such a screening program, detection of affected fetuses is almost always via identification of a newborn who is thrombocytopenic and discovering that it is due to FNAIT from a serological workup.5 The first baby affected in a family may suffer an intracranial hemorrhage; if so, the second infant would be at very high risk of also having this serious complication of FNAIT.6

What is the current approach to this situation (ie, a second affected pregnancy with FNAIT)? The current approach is to treat the mother with high-dose intravenous immunoglobulin with or without prednisone to try to decrease the impact of the antiplatelet antibody on fetal platelets. If the treatment is stratified according to the severity of FNAIT in the previous fetus, then this seems to work very well but it does require considerable treatment, which over the course of a pregnancy could be quite expensive.7

Ghevaert et al started work years ago on an anti-fetal human platelet antigen-1a (HPA-1a) antibody that they have modified by changing the Fc portion so that it will not mediate platelet destruction. Even though the antibody will bind to platelets, it will not engage FcγRI, FcγRIIA, or FcγRIIB. Therefore, platelets sensitized with this modified anti–HPA-1a antibody are not cleared and destroyed. Previous studies in vitro and in animals have shown that the modified antibody can effectively block FcγR binding.
REFERENCES

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Trick to treat: tricking the thymus to treat cancer

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In this issue of Blood, Schmitt et al address the biology and safety of T cells engineered to express T-cell receptor (TCR) variants endowed with enhanced affinity for tumor-associated antigens.1

The authors hypothesize that the negative selection of high-affinity self-reactive thymocytes might overprotect against self-reactivity and result in the maturation of T cells with low-affinity TCR and suboptimal recognition of tumor-expressing, nonmutated self-antigens. This notion is supported by the finding that TCRs that bind viral nonself antigens fall within higher affinity ranges when compared with those that bind tumor–related antigens.2 As high-affinity T cells bear the potential to respond to minute antigen expression, efforts have been focused on the retrieval and/or the engineering of high-affinity tumor-specific T cells for adoptive cellular immunotherapy. Thanks to increasing knowledge of TCR engineering, it is now possible to design increased-affinity variants of any given TCR and to engineer patient T cells to recreate potent high-affinity tumor-directed T-cell responses.3 The potential to artificially increase the affinity of any given TCRs and express them on patients’ autologous lymphocytes, however, raises important questions: Could thymic mechanisms of negative selection be tricked into improving tumor recognition and, thus, the efficacy of cancer immunotherapy? And could T cells expressing an enhanced-affinity TCR bypass the affinity limits imposed by thymic selection and be safe, or are they potentially at risk to mediate autoimmune manifestations?

To begin addressing these questions, Schmitt et al engineered mature T cells with TCR variants with enhanced affinity for cognate peptides derived from WT1 and Mesothelin, two highly relevant unmaturated self-antigens that are overexpressed in several tumors and are linked to oncogenesis and tumor progression.4,5 The results described show that such engineered T lymphocytes can be infused into mice without causing autoimmune tissue inflammation or damage, even after their terminal differentiation into cytolytic effectors in response to pathogenic antigen-expressing Listeria monocytogenes. Thus, limits imposed by negative selection in the thymus could be safely overcome by the genetic manipulation of mature cells (at least in the case or WT1 and Mesothelin) (see Figure). Of note, when expressed in developing precursors, using the retrogenic technique, high-affinity TCR resulted in negative selection of cells with...
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