Keeping track of AID

A DNA-mutating enzyme that fine-tunes B cell antibody specificity can become a dangerous liability if its activity is mistimed, misplaced, or left unchecked. Crouch et al. (page 1145) have now designed a mouse model to track the enzyme’s activity in B cells during development and immunity. The model can now be used to determine how the enzyme’s destructive force is controlled.

The enzyme in question is AID (activation-induced cytidine deaminase), which converts cytidines to uracils. AID activity within activated B cells allows them to better recognize a pathogen by creating mutations in the variable regions of their immunoglobulin (Ig) genes. AID-assisted recombination within Ig constant regions also allows B cells to generate different types of antibodies. Mismatch repair mechanisms then splice out the mutations, reseal the new ends, and thereby create new sequence variants at the Ig loci. But this AID clean-up machinery is itself error-prone and increases the likelihood of further mutations that make the animal vulnerable to diseases such as cancer.

To monitor the expression of AID in vivo, the team designed transgenic mice that express a fluorescent protein upon AID activation that then permanently marks all AID-expressing cells and their progeny. AID was not expressed by developing B cells. It was first switched on in activated B cells that were beginning to proliferate in germinal centers (GC)—the hub of the B cell immune response.

The switch seems to be controlled by a short DNA sequence immediately downstream of the AID gene. This sequence had more histone acetylation (which marks transcriptionally active regions) in activated B cells. Deleting the sequence almost completely abolished AID expression. AID expression was down-regulated as B cells differentiated into either memory cells or antibody-producing plasma cells and began to leave the GC. The exact mechanism that shuts off AID in exiting B cells remains to be worked out. Using this model to resolve this mechanism and understand how AID regulatory mechanisms get derailed in B cell cancers is the team’s next step. JEM

Avoiding fetal loss

A pregnancy disorder that leads to an early loss of the fetus is linked to mutations that increase the mother’s tendency to form blood clots. But Sood et al. (page 1049) now find that maternal genes are only partly responsible. The rest of the blame falls on genetic defects that the fetus inherits from the father.

Recurrent miscarriages are associated with mutations known as Leiden polymorphisms, which prevent the factor V coagulant from being destroyed by the anticoagulation machinery. The assumption has been that clots formed in the placenta of Leiden mothers might cripple fetal growth by blocking nutrient supply.

Examination of placental tissue from Leiden mothers, however, shows no correlation between placental clotting and fetal loss. And female mice with Leiden mutations give birth successfully despite their propensity to form blood clots.

Sood et al. predicted that risk factors from the father might increase the risk of fetal loss. They found that crossing Leiden female mice with males that had mutations in anticoagulation factors now caused the loss of only those fetuses that were less able to break down maternal factor V. The synergy between maternal and fetal defects suggests that screening both parents for anticoagulant mutations may be a better indicator of high-risk pregnancies than screening only the mother.

The mouse fetal losses were not due to placental clotting, but fetal loss was prevented by blocking the activation of the mother’s platelets. The authors hypothesize that fetal loss must involve an as yet unknown action of maternal platelet factors on the fetal cells at the interface of maternal and fetal tissue. JEM