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Getting rid of nonsense

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Many human diseases are caused by point mutations that affect RNA splicing. It has been observed that nonsense mutations that generate premature termination of translation products can drive the use of alternative splicing to rescue protein function. In the July 5 Science, Wang *et al.* describe the affects of nonsense mutations on splicing of the T-cell receptor-β (*TCRβ*) gene (*Science* 2002, **297:**108-110). The *TCRβ* gene often acquires nonsense point mutations because of its rearrangement during T-cell development. They discovered an alternatively spliced transcript, alt-mRNA, generated by an alternative splice acceptor and donor, that skips the deleterious mutation. Introduction of several random nonsense mutations increased alt-mRNA levels, whereas missense and silent mutations did not. Frameshift mutations that create a downstream nonsense codon also upregulate alt-mRNA. Wang *et al.* conclude that the regulation is specific and not due to disruption of splicing-regulatory elements. They found that alt-mRNA regulation required a transfer-RNA-dependent scanning mechanism. These results link translation signals to the regulation of alternative splicing in the nucleus.

References

1. The regulation of splice-site selection, and its role in human disease.

2. *Science*, [http://www.sciencemag.org]