LYMPHOCYTE DEVELOPMENT

Out of sync

Central to Burnet's clonal-selection theory was the 'one lymphocyte, one antigen receptor' rule. With rare exceptions, we now know this to be true. But how is this achieved when for each antigen-receptor chain there is the choice of two alleles? Carefully regulated expression of the enzymes mediating T-cell receptor (TCR) and B-cell receptor (BCR) gene rearrangement is thought to be crucial, and now a report in *Nature* indicates that asynchronous replication of antigen-receptor genes might have a key role.

Allelic exclusion is not unique to the immune system. Olfactory receptor genes and the X chromosome in females are both monoallelically expressed, and these are known to replicate asynchronously — leading Mostoslavsky and co-workers to ask whether this is also true of immunoglobulin and TCR loci.

The technique of fluorescent *in situ* hybridization (FISH) allows replicating loci to be detected as a double dot; finding both a double and single dot during interphase is characteristic of an asynchronously replicating gene. Using this method, the authors found that the immunoglobulin κ, λ and μ loci, and the TCRβ locus replicate asynchronously in both lymphoid and non-lymphoid cells. Further studies of the κ locus in mature B cells showed that the non-expressed, germ-line copy consistently replicates late. By examining fibroblasts from mice heterozygous for a linked marker gene they confirmed that the selection of the early replicating κ allele — maternal or paternal — is entirely random, and once established is stable within a clone.

So, when is this asynchronous replication of antigen-receptor loci established? To address this question the authors examined κ-locus replication in the very earliest stages of ontogeny. Immediately after fertilization, during the first cell division of the zygote, there is asynchronous replication of the κ locus, which seems to be inherited from the gametes. At later stages of embryogenesis (morula and blastula), the κ alleles replicate at the same time, but in embryonic stem cells and later developmental stages there is asynchronous replication. Interestingly, this developmental pattern mirrors that of X-chromosome inactivation.

The authors propose that the early replicating allele will have a head start, and become accessible to the rearrangement machinery first. Contrary to some prevailing models, these results imply that the availability of antigen-receptor alleles for rearrangement is not equivalent. The temporal advantage conferred by early replication might be crucial in allowing a single antigen receptor to be sucessfully formed and tested at the cell surface, before a competing receptor can be generated.

Jennifer Bell

References and links

ORIGINAL RESEARCH PAPER Mostoslavsky, R. *et al.* Asynchronous replication and allelic exclusion in the immune system. *Nature* **414**, 221–225 (2001)

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