fibrosis syndrome termed bronchopulmonary dysplasia in human premature infants[11]. That perinatal antagonism of excess TGF-β can rescue the alveolar hypoplasia in fibrillin-1 deficiency buttresses the argument that therapeutic approaches to maintaining correct levels of TGF-β activity could perhaps prevent alveolar hypoplasia.

Matrix matters

The loss of microfibrils as a result of defective fibrillin-1 markedly changes the targeting and sequestration of latent TGF-β. This leads to the pronounced TGF-β activation that triggers the developmental inhibition of alveolarization that presents eventually as emphysema. Notably, abrogation of LTBP-4 (which specifically binds TGF-β1) also leads to profound defects in the elastin fiber structure and pulmonary emphysema[12]. Sterner-Kock *et al.*[12] speculated, however, that the emphysema resulted from reduced deposition of TGF-β in the extracellular space in the lung parenchyma. In sum, these findings point to the key role of binding proteins in control of the activity of TGF-βs as well as in mediating precise local concentration of the cytokine.

During cardiac development, TGF-β signaling induces endocardial transformation that is required for proper formation of the endocardial atrioventricular cushions and subsequently atrioventricular valves[13]. In Marfan syndrome, atrioventricular valves frequently have pathologic (myxomatous) changes associated with abnormal reorganization and production of extracellular matrix proteins, collagen and proteoglycans[14]. As TGF-βs are well known inducers of extracellular matrix deposition, it is tempting to speculate, as suggested by Neptune *et al.*[5], that there is a causal relationship between the aberrant activation of TGF-β by dysfunctional fibrillin-1 and myxomatous valve changes in Marfan syndrome.

The precise mechanism by which fibrillin-1 controls TGF-β activation is still unknown. It has been previously shown that fibrillin-1 interacts with LTBP-1 (and LTBP-4) in a tissue-specific fashion[15]. Future studies are needed to show whether the fibrillin–LTBP interaction is needed to protect the LLC from proteolytic activation or whether fibrillin-1 functions more directly in controlling assembly or stability of latent TGF-β complexes. □

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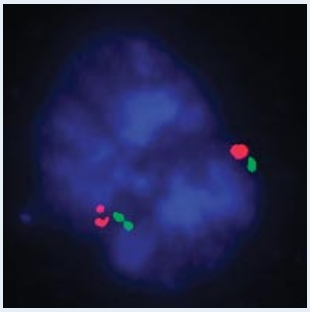
Connecting the dots

Genes that are expressed from a single allele in a random manner have one allele replicated earlier than the other. A new study shows that this replication asynchrony is coordinated within chromosome pairs.



The accompanying photograph seems at first glance to capture a straightforward fluorescence *in situ* hybridization experiment, with each colored dot representing a tagged probe bound to a particular locus. But the details of the data tell an intriguing story. The image is taken from findings presented on page 339 by Nandita Singh and colleagues showing that chromosome-pair non-equivalence is not limited to the specific instances of imprinting and X-chromosome inactivation but may be much more widespread, at least in the mouse genome.

The results of Singh *et al.* are part of a line of work on the replication timing of a group of genes that are expressed monoallelically in a random manner (genes that are expressed from either the paternal or maternal chromosome, with variation from cell to cell). Such genes are represented in several gene families, including odorant receptors and T-cell receptors. Whereas most genes are replicated synchronously, monoallelically expressed genes are asynchronously replicated in S phase. As these genes are scattered throughout the genome, Singh and colleagues asked whether the observed asynchronous replication was coordinated in any way.

The answer is found in this picture and in others like it. In this particular mouse embryonic fibroblast, the red dot corresponds to the odorant-receptor gene *Olfr1* and the green dot to the odorant-receptor gene *Olfr10*, which are 14 cM apart on chromosome 11. The linked double-dot signals on the left indicate that the early-replicating allele for each gene is on the same chromosome. Notably, this coordination holds true for several monoallelically expressed loci on chromosomes 2, 6 and 7 as well, and is not limited to odorant-receptor genes.

That these loci are distant from each other along a chromosome, with many intervening genes that replicate synchronously, suggests some kind of 'spooky action at a distance,' to borrow a phrase from quantum mechanics. Although the coordinated replication of these scattered alleles is in some ways more perplexing than whole-chromosome X inactivation, the authors suggest that similar mechanisms may be involved. —Alan Packer