

Akt is a protein kinase that functions downstream of insulin receptor substrate in the insulin signaling cascade. Sabio *et al.* found that Akt activation was attenuated in the liver, skeletal muscle, and adipose tissue of wild-type mice fed a high-fat diet, whereas ablation of JNK1 in adipocytes restored the effect of insulin in adipose tissue (possibly by preventing JNK1-mediated phosphorylation of insulin receptor substrate). However, the authors observed that both the impairment of Akt activation in response to a high-fat diet, and impairment of the suppressive effect of insulin on glucose production in the liver, were ameliorated in mice with JNK1 deficiency in adipocytes.

Among various pro- and anti-inflammatory cytokines, as well as adipocyte-derived hormones thought to regulate insulin sensitivity, Sabio *et al.* found that only the abundance of IL-6 was substantially affected in mice with adipocyte-specific deficiency of JNK1. Increases in the serum concentration of IL-6 and in the production of this cytokine in adipose tissue that are induced by a high-fat diet were almost completely eliminated by the ablation of JNK1 in adipocytes. SOCS3, a signaling molecule that is activated by IL-6 in hepatocytes, inhibits insulin signal transduction (8). Expression of SOCS3 in the liver increased when wild-type mice were fed a high-fat diet, and this effect was prevented by JNK1 ablation in adipocytes, suggesting that increased SOCS3 expression induced by IL-6 contributes to the development of hepatic insulin resistance.

Sabio *et al.* have clearly shown that JNK1 in adipocytes of obese animals regulates the circulating concentration of IL-6, which in turn likely plays an important role in the pathogenesis of insulin resistance. Although this study uncovers the crucial role of stress signaling in adipocytes during “fat inflammation,” it does not exclude a role for macrophages in adipose tissue in obesity-induced insulin resistance. Several studies have indicated the importance of M1 macrophages in the development of obesity-induced insulin resistance (9–11). Also, the findings of Solinas *et al.* (12) contradict those of Sabio *et al.* in that ablation of JNK1 in myeloid cells ameliorated obesity-induced insulin resistance. Although the reason for this discrepancy is unclear, the results of Solinas *et al.* have also been challenged (13). Moreover, adipocytes and macrophages may influence each other's functions, with adipocytes promoting the conversion of M2 macrophages to the M1 phenotype (10, 11). Interactions between adipocytes and macrophages thus likely trigger inflammation in adipose tissue, with both cell types

contributing to the development of obesity-induced insulin resistance (see the figure).

Although Sabio *et al.* found that the extent of macrophage infiltration in adipose tissue was not altered by the ablation of JNK1 in adipocytes, it may be that the ratio of M1 to M2 macrophage cells was affected. Their study underscores the prominent role of IL-6 among cytokines in the pathogenesis of insulin resistance. Given that IL-6 exerts a glucose-lowering effect when acting in a paracrine manner in the liver (14), it is possible that a pronounced systemic increase in IL-6 abundance and a smaller local increase in the concentration of this cytokine exert opposite effects on glucose metabolism. Although the data of Sabio *et al.* indicate that adipose tissue is responsible for an increase in the circulating concentration of IL-6 in obese animals, whether adipocytes or macrophages are the source of this cytokine is not yet clear. It will thus be of interest to assess the effects of IL-6 ablation specifically in adipocytes or in myeloid cells on obesity-induced insulin resistance. Tocilizumab, a monoclonal anti-

body that inhibits the binding of IL-6 to its receptor, is currently in clinical trials for treating inflammatory diseases, including rheumatoid arthritis (15). This drug might also prove effective for the treatment or prevention of type 2 diabetes.

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EVOLUTION

Competitive Centromeres

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Divergence in DNA sequence associated with a common chromosomal element is linked to fitness and evolution of a wild species of flower.

A case of strongly distorted genetic ratios in hybrids between two species of the monkeyflower *Mimulus* seems to be due to a competitive advantage of one version of a chromosome over its partner's homologous region during female gamete formation. On page 1559 of this issue, Fishman and Saunders (1) provide cytogenetic and genetic evidence implicating the centromere region of this chromosome. In most eukaryotes, segregation of chromosomes during cell division is controlled by the centromere regions. The new study suggests that the more competitive type of centromere spread recently in one of the species, *M. guttatus*, but not throughout the whole species, as one might have expected from its strong advantage. There may thus be some counterbalancing disadvantage. This system may advance our understanding of centromere behavior.

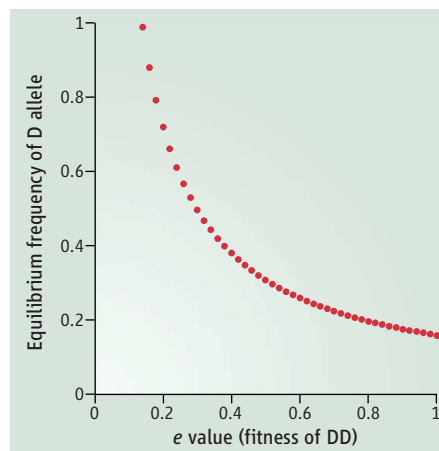
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In diploid eukaryotes, each parental individual contributes to a progeny one of two copies of each gene, and each progeny has a 50% chance of receiving each of the two allelic versions of the gene, giving the familiar 1:1 Mendelian ratio. But non-1:1 ratios of segregating alleles have been observed in several situations, including in offspring derived from crosses between different species. Often, this may be caused by nothing more than the presence of recessive (or nearly recessive) deleterious mutations in the parent species. Descendants (F_2) of the first generation (F_1) of offspring can thus become homozygous for two mutant alleles of such genes, leading to a deficit of this diploid genotype and of genetic markers closely linked to loci carrying such mutations (2). Such situations are helpful for studying the genetic basis of incompatibilities between different species when genes from the two species interact in ways that cause deficits of some genotypes (3). These incompatibilities are sometimes asymmetrical, differing between the reciprocal crosses—for instance,

when the diploid genome of one parent is incompatible with a maternally transmitted genome from the other; asymmetry can also appear in the first generation of offspring (4).

A completely different way in which non-Mendelian ratios can occur is when the different alleles in a heterozygous genotype, such as a hybrid, have different probabilities of forming gametes. In normal female meiosis in plants and animals, only one of the four products forms an egg nucleus while the other three are discarded into polar bodies. There might then be competition for inclusion in the egg nucleus. A successfully competing allele will be present in more than 50% of the eggs of heterozygotes, although the gametes of both kinds can function in homozygotes. An example is known in mammals, when mothers heterozygous for centric fusions between two chromosomes transmit mostly unfused chromosomes to their progeny (5). These situations with distorted segregation ratio among the gametes are called meiotic drive (6); other cases include the “selfish” preferential transmission of heterochromatic knob-bearing copies of chromosome 10 in maize, and supernumerary (B) chromosomes in many organisms (7).

Although selfish preferential transmission of centromeres and competition between centromeres have been the focus of recent interest (8–10), much of the inference is circumstantial and relies on evidence for evolutionary “arms races” between centromeres and the proteins that bind to them (perhaps to resist preferential segregation). The discovery of distorted transmission in a cross between *M. guttatus* and *M. nasutus* (11) gave promise that mechanistic details could be elucidated, because *Mimulus* species offer good opportunities for genetic and molecular studies (12). Fishman and Saunders noted that transmission ratios of some genetic markers were highly distorted when F_1 plants were pollinated by either parent species. This cannot have been attributable to pollen competition (because ratios were normal in progeny using F_1 pollen) or to mortality of zygotes (which would distort ratios regardless of whether the F_1 parent was the seed or the pollen parent). Inviability of some female gametes or segregation distortion—as seen in male *Drosophila* fruit flies (a well-studied system), in which half of the sperm of heterozygotes are defective (8)—are also unlikely because fertility was normal. A competitive effect acting in female gamete formation is therefore the most likely cause of distortion. The most distorted ratios were found at genetic map position 30 in linkage group 11, but statistically significant distortion remained for markers many



Allele frequency. The plot shows the frequency of the D allele predicted in a population that has reached equilibrium, using the equations in Fishman and Saunders (1). The plot shows the frequency values for a distortion of $d = 8\%$ and a range of male fertility disadvantages to DD homozygous plants (x axis). A disadvantage (e) greater than about 13% prevents the D allele from spreading through the whole population, and a disadvantage of around 30% is needed to produce an equilibrium population with a frequency of the D allele similar to that estimated for the *M. guttatus* population; this is remarkably good agreement between the theory and the estimated disadvantage.

centimorgans distant. This pattern suggests that this chromosome carries a distorting factor, D, that is transmitted to about 98% of the egg nuclei (11).

What is the D factor and how does it distort? The high degree of distortion suggested that the centromere might be competing for inclusion in the egg nucleus. Fishman and Saunders boldly opted for a cytogenetic approach to test this hypothesis. They searched the *M. guttatus* genome sequences for candidate centromeric repeats, on the basis of similarity to those of other plant species. In their fluorescence in situ hybridization experiments, a common repeat sequence indeed hybridized to the centromeres of the chromosomes of the *M. guttatus* parent of the hybrid, and one chromosome pair had a distinctive double-banded appearance. This chromosome corresponds to linkage group 11; when the authors tested one of the strongly distorted genetic markers on chromosome preparations, it too hybridized near the double-banded centromere region.

One hypothesis for D is that it is merely a normal allele that outcompetes a weak version that evolved in the self-fertilizing species *M. nasutus*. However, this seems unlikely, because D has clearly spread recently in the *M. guttatus* population and is still polymorphic; of nine *M. guttatus* inbred lines tested, four yielded F_1 hybrids with *M. nasutus*

showing no transmission distortion of a marker allele (at a microsatellite locus, *aat356*, in the strongly distorted chromosome region). Moreover, three of the nondistorter strains were examined cytologically and did not have the double-banded centromere.

Is this polymorphism merely a transient state, or does the D allele have disadvantages that prevent its becoming fixed in the population, thus maintaining it in a polymorphic state? To answer this, Fishman and Saunders estimated the distortion within the *M. guttatus* population. Distortion does occur, but much less than in hybrid plants (heterozygotes mated to non-D plants produce 58% D progeny). A population genetic model of a distorting allele suggests that such distortion would cause rapid spread into a population. Indeed, the authors found that chromosomes with the D allele were highly homogeneous in the alleles carried at several loci in the same region of the genetic map, just as expected if this allele has recently increased to a high frequency, whereas at the loci examined (up to 45 kb from the *aat356* locus), the non-D chromosomes included a diversity of alleles. With the rough estimates of the two governing parameters of the model (degree of distortion $d = 8\%$, fitness disadvantage $e = 20\%$), the predicted equilibrium D frequency is much higher than the estimated frequency, but higher e values rapidly lower the discrepancy (see the figure). It will be interesting to analyze the diversity in this genome region more quantitatively, using methods that can test for balancing selection (13). If balancing selection is detected, perhaps there are indeed additional disadvantages. Now that genetic resources in *Mimulus* have been developed, this wild plant system may, surprisingly, provide rich information about centromere behavior.

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