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Tracking Down a Cheating Gene

Some genes will play dirty to gain a selective advantage

Barry Ganetzky

In 1956, Yuichiro Hiraizumi, a graduate student in the laboratory of James F. Crow at the University of Wisconsin, made a remarkable discovery that contradicted a basic tenet of genetics—the principle that each chromosome of a pair has an equal chance of being passed on to the next generation. Hiraizumi was carrying out genetic studies of natural populations of the fruit fly *Drosophila melanogaster*, with the nominal goal of investigating genes affecting viability.

In these experiments, Hiraizumi crossed white-eyed females with red-eyed males. The females were from an inbred laboratory strain, and both members of the relevant chromosome pair carried certain mutations that produced the white eye color. The members of the corresponding chromosome pair in the males were dissimilar. One chromosome was from the laboratory strain carrying the mutations for white eyes. The other chromosome of the pair was from wild-caught flies and carried the genes for normal red eye color. These eye-color genes merely served as convenient genetic markers enabling Hiraizumi to trace the transmission of each of the two chromosomes from the males to the next generation.

Barry Ganetzky is the Steenbock Professor in Biological Sciences in the Laboratory of Genetics at the University of Wisconsin-Madison. He received his Ph.D. at the University of Washington in Seattle in 1976 and was a postdoctoral fellow at the California Institute of Technology until 1979, when he accepted his current position. Although his research focuses primarily on molecular and genetic studies of neuronal signaling in Drosophila, *he continues to study the segregation distortion system, in which he has had a long-standing interest. Address: Laboratory of Genetics, 445 Henry Mall, University of Wisconsin, Madison, WI 53706. Internet: ganetzky@facstaff.wisc.edu*

According to the principles of inheritance, roughly half of the offspring from these matings should have been red-eyed, and the other half white-eyed. That's not what happened. Quite unexpectedly, a few of the mating pairs produced only red-eyed offspring. These crosses flagrantly violated genetic law: The chromosome carrying the red-eye genes (the one derived from nature) was transmitted preferentially to the offspring, whereas the other member of the chromosome pair, the one carrying the white-eye mutations, seemed not to be transmitted at all.

The name *Segregation Distorter* (*SD*) was given to chromosomes that display this unusual pattern of transmission, and geneticists now know that roughly 3 to 5 percent of nearly every natural population of *Drosophila melanogaster* harbors *SD* chromosomes.

But the very notion that such transmission distortions can take place is disturbing to anyone who considers questions of evolution and natural selection. In theory, evolution by natural selection is a rigorous process that favors the retention of genes that enhance the ability of organisms to survive and reproduce. Chromosomes and the genes they carry are supposed to be meted out equally into eggs and sperm through the specialized cell divisions called *meiosis*. Proper meiosis ensures competing genes equal representation in the gametes and thus guarantees that each gene is exposed equally to the forces of selection.

A particular gene that figured out a way to beat the system by ending up in the vast majority of functional gametes would have an enormous but unfair advantage over competing genes. Such cheating genes would tend to increase in a population even if they conferred no selective advantage—or, indeed, were harmful to the organisms in which they were present. In principle, a situation like this could lead to the extinction of a population.

The potent impact such genes could have on natural populations was first pointed out in 1957 in a theoretical paper by Laurence M. Sandler and Edward Novitski of Oak Ridge National Laboratory. They coined the phrase "meiotic drive" to refer to any alteration of meiosis that resulted in excess transmission of one genetic variant over its alternative. The definition has now been expanded to include any alteration in meiosis or the subsequent production of gametes that results in preferential transmission of a particular genetic variant.

Examples of meiotic drive have now been discovered in a wide variety of organisms, including fungi, higher plants, insects and mammals. The mechanisms by which these various meiotic-drive systems operate remain almost a complete mystery. However, members of my laboratory have recently made substantial progress in unraveling one of them—the *SD* system—the very one discovered by Hiraizumi more than 40 years ago.

Fateful Meetings

Hiraizumi wisely forgot about the original purpose of his experiments and focused instead on the analysis of the serendipitously discovered *SD* chromosomes. By chance, it happened that Sandler had made arrangements to join the Crow laboratory as a postdoctoral fellow even before *SD* was discovered. When it became evident that *SD* represented an actual instance of meiotic drive, which Sandler had considered from a theoretical standpoint only, he quickly

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Figure 1. Red-eyed fruit flies were unexpectedly over represented among the offspring of a particular genetic cross predicted to yield roughly equal numbers of white-eyed and red-eyed progeny. This result, obtained by Yuichiro Hiraizumi more than 40 years ago, led to his discovery of *segregation distortion*, where one chromosome is preferentially transmitted to offspring over its partner chromosome. Eye color, as it turns out, is just a convenient marker that allows geneticists to observe such distortions in chromosomal transmission. Over the years, biologists have come to identify the precise genes responsible for segregation distortion and are starting to learn the details of the mechanism as well.

teamed up with Hiraizumi to delve further into the phenomenon.

Over the next several years, Hiraizumi and Sandler provided the framework for the basic understanding of the phenomenon of segregation distortion, on which all subsequent investigations, including my own, have been built.

It did not take long for the two to establish that *SD* acted only in males; transmission from females was in accord with genetic law. The team also showed that distortion did not depend particularly on the laboratory strain used in the original crosses, since distortion could also be observed when a variety of other chromosomes were paired with *SD*. Furthermore, the two demonstrated that distortion did not happen as a result of increased mortality of embryos that inherited the non-*SD* chromosome. Rather, they concluded that distortion was related to a dysfunction in the sperm. That is, some of the sperm (those bearing the non-*SD* chromosome) in these distorting males failed to develop or function properly and did not participate in fertilization at all.

Most important, Hiraizumi and Sandler showed that distortion was not a property of the *SD* chromosome itself, but was caused by at least two discrete genes with distinct roles. In later studies, Daniel L. Hartl at the University of Minnesota expanded and clarified the definition of the two key components of the *SD* chromosomes.

One of these elements is called *Sd*, a particular gene carried on *SD* chromosomes. *Sd* was defined as the gene primarily responsible for causing distortion. The other element is called *Responder (Rsp)* and was defined as the apparent target of distortion. At least three distinct variants of *Rsp* have been found in nature and in laboratory strains: Rsp^{i} *(Responder insensitive)* is found on all *SD* chromosomes, as well as on some non-*SD* chromosomes; Rsp^{s} *(Responder sensitive)* is found on chromosomes that *are* sensitive to the action of *Sd;* and Rsp^{ss} (*Responder supersensitive*), is particularly sensitive to distortion.

Following the initial observations by Hiraizumi and Sandler, studies by several other investigators helped to fill in pieces of the puzzle. James W. Peacock and John Erickson, working at the University of Oregon, demonstrated that meiosis itself proceeds normally in distorting males—chromosomes segregate and are apportioned normally into the immature sperm cells called *spermatids*. Careful measurements by Hartl and Hiraizumi and by Benedetto Nicoletti and Gianni Trippa at the University of Rome confirmed sperm dysfunction as the ultimate basis of distortion.

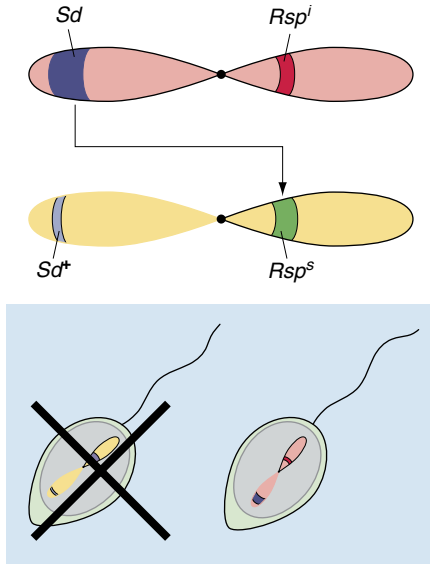

Figure 2. Chromosomes come in pairs, and classical laws of inheritance predict that each one of the pair has an equal chance of being transmitted to the next generation. This is assured by meiosis, the specialized cell divisions in which the gametes—sperm and eggs—are formed and during which one chromosome of each pair is segregated into a cell destined to become a sperm or an egg. A male fly that carries one chromosome with genes specifying white eyes *(yellow chromosome)* and another with genes specifying red eyes *(red chromosome)* produces two classes of sperm; each type carries one of these chromosomes. In this example, the female carries genes for white eyes only and therefore has two similar chromosomes. An embryo resulting from the union of sperm *a* and either egg *c* or *d* contains genes for white eyes, which will yield white-eyed flies. The union of sperm *b* with either egg gives rise to embryos carrying one of each chromosome and, because red eyes are dominant, will yield red-eyed flies. Under normal circumstances, then, roughly 50 percent of the offspring would be expected to have white eyes, and the other 50 percent would have red. This is not the case for the offspring of segregation-distorting males. White-eyed offspring are rarely seen. Almost all of the progeny are red eyed. In Hiraizumi's experiment, the chromosome carrying the red-eye genes was derived from wild-caught flies, as opposed to laboratory strains of flies. As Hiraizumi discovered, a small fraction of flies in natural populations harbor these unusual chromosomes that are able to promote their own transmission at the expense of their partner chromosome.

Distorting males produce only half as many progeny as normal males even though the embryos produced with their sperm do not experience a greater rate of mortality. The decrease in progeny therefore implied that, compared with normal males, distorting males generate only half as many functional sperm, the vast majority of which contain the *SD* chromosome and not the homologue. The other half of the sperm—those that received the non-*SD* chromosome—are eliminated or are otherwise rendered unable to participate in fertilization.

Fratricide

Taken together, these results all indicate that *SD* manifests its effects during the time that the immature—but seemingly normal—spermatids mature into fully functional sperm. What goes wrong between formation of spermatids by meiosis and their subsequent maturation to sperm? The answer was provided by electron-microscope studies of sperm maturation by Kiyoteru T. Tokuyasu and his colleagues at the University of California, San Diego.

In the course of normal maturation, just before sperm acquire their characteristic elongated cell bodies and their tails, the chromosomes become extremely condensed within the highly compacted sperm nucleus. However, Tokuyasu and his colleagues found that in distorting males the chromosomes in precisely half of the spermatids fail to condense and instead remain dispersed. These spermatids are unable to form mature, viable sperm.

The general interpretation that emerges from these results is that in distorting males, the *SD* chromosome produces a deleterious effect on its partner chromosome. Spermatids that receive this partner chromosome then fail to mature properly, whereas spermatids that receive the *SD* chromosome develop normally and carry the *SD* chromosome into the next generation.

From this perspective, *SD* chromosomes have managed not merely to cheat the system, but to do it in a diabolical manner worthy perhaps of Shakespeare—they eliminate the competition by fratricide.

In spite of having this general understanding of the basis of distortion, biologists would like to know how, on a molecular level, these events transpire. We would like to know how the specific genes involved—*Sd* and *Rsp*—

interact. And to understand that, we need to know what products these genes encode. Only when we have answered these questions can we fully unravel the mystery of *SD*. These are the questions we are now trying to answer in my laboratory.

Responders

Our recent results are the outcome of studies that I began more than 20 years ago, when I was a graduate student in Sandler's laboratory at the University of Washington. I set out to generate chromosomes from which either the *Sd* or the *Rsp* gene was deleted by exposing the chromosomes to x rays. The resulting small deletions would be useful in precisely pinpointing the chromosome location of these genes and in characterizing their functional properties.

I showed that when the *Sd* gene was deleted from an *SD* chromosome, the deleted chromosome was no longer able to distort a sensitive partner chromosome; both chromosomes were then transmitted to offspring in normal ratios. This result demonstrated that the *Sd* mutation caused some new function to be acquired. (This is in contrast with most genetic mutations, which cause some normal function to be lost.) When the gene producing this novel activity was completely eliminated by a deletion, an otherwise intact *SD* chromosome lost all ability to cause distortion.

Furthermore, when Rsp^s was deleted from the partner chromosome, it was no longer subject to distortion by *SD*. Instead, it was transmitted normally, as though it carried the Rsp^i gene. These results supported the idea that as a consequence of some action of *Sd*, the chromosomes in a spermatid nucleus that receive the Rsp^s gene fail to condense properly during sperm maturation. A chromosome that entirely lacks *Rsp* is immune to the effects of *Sd*. Interestingly, *Rsp* does not appear to have any essential function of its own. Even flies that are missing *Rsp* from both chromosomes are viable and fertile.

Additional studies allowed me to determine exactly where on the chromosome these genes lie. *Rsp* turns out to be very close to the center of the chromosome, near a structure called the *centromere*, which is important for chromosome movement during cell divisions—during, for example, meiosis. This particular chromosomal region contains mostly *heterochromatin*, highly repetitive, simple DNA sequences that generally do not code for protein. Nevertheless, heterochromatin constitutes about one-third of the total length of the chromosome. The precise function of heterochromatin is still unknown, although it is thought that this region has some structural role and may be involved in meiosis.

The location of *Rsp* in heterochromatin was consistent with its genetic behavior as some kind of target for the action of *Sd*, rather than as a typical gene encoding a protein product.

This result was confirmed by a molecular analysis by Chung-I Wu at the University of Rochester and Terrence W. Lyttle at the University of Hawaii. They successfully cloned and sequenced *Rsp* and showed that it does not code for a protein. Instead, *Rsp* is composed of a simple DNA sequence, containing 120 nucleotide bases, repeated over and over again for its entire length. Furthermore, they found that the sensitivity of *Rsp* to the action of *Sd* is a direct consequence of the number of times this sequence is repeated. The insensitive variant of *Rsp*, Rsp^i, contains fewer than 50 copies of this sequence. The sensitive variant, Rsp^s, contains several hundred copies, and the supersensitive variant, Rsp^{ss}, contains about 1,000. The sensitive variants are so large that Sergio Pimpinelli and Patrizio Dimitri at the University of Rome have shown that these DNA segments can be seen under the microscope as a discrete blocks of heterochromatin.

Distorters

At the same time that other laboratories were learning about *Responder*, people in my lab were trying to understand the other half of the problem. We were trying to make sense of *Sd*—the key gene required for distortion. This was difficult, since we had no idea what the gene looked like and didn't know whether we would recognize it if we did in fact come across it.

On the basis of its genetic properties, we anticipated that the mutant gene—*Sd*—would differ from its normal counterpart—Sd^+—by more than just a single nucleotide base. We believed the difference to be more substantial, and therefore that it could be readily discerned by standard molecular biological methods. Using cytogenetic techniques, John B. Brittnacher extended my original deletional analysis and identified a chromosome segment of roughly 200,000 bases

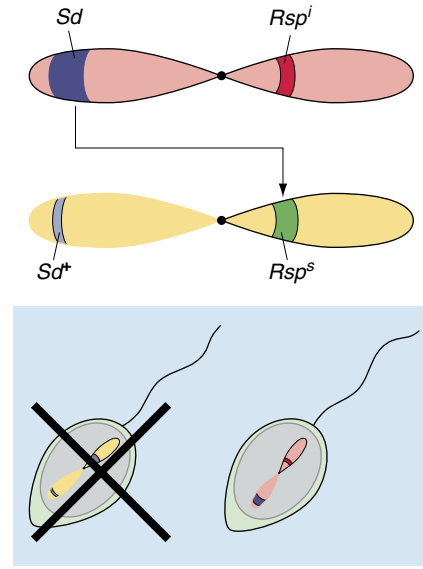

Figure 3. Segregation distortion requires the interaction of two genetic factors. The distorting chromosome carries a gene called *Sd*, here represented by a violet band (the normal counterpart of this is Sd^+, represented by the lavender band). The chromosome that is eliminated carries a sensitive responder region (*green band*), called Rsp^s (the counterpart to this is Rsp^i, *red band*). Other studies demonstrated that distorting males—those that carry the *Sd* gene—produce little or no viable sperm containing chromosomes bearing Rsp^s.

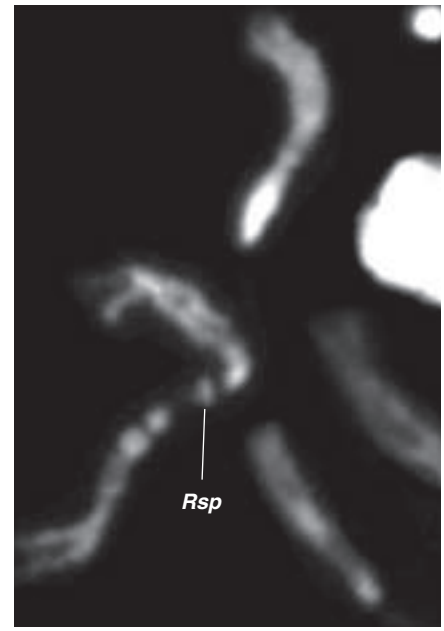

Figure 4. Sensitive *Responder* region contains many more copies of a particular short, repeated DNA sequence than is present on insensitive *Responder*-bearing chromosomes. Rsp^s is so large, in fact, that it can be distinguished cytologically as a distinct band when stained with appropriate chromosomal dyes. (Micrograph courtesy of Sergio Pimpinelli, the University of Rome La Sapienza.)

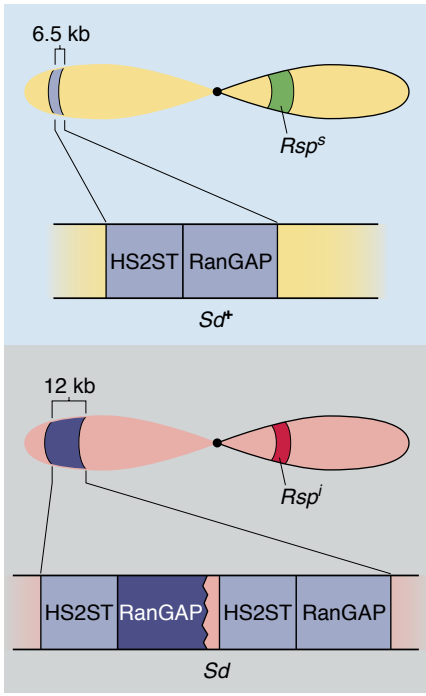

Figure 5. Nature of *Sd*⁺ and *Sd* is revealed through molecular analysis. On normal chromosomes, the DNA segment that includes *Sd*⁺, which encodes the RanGAP protein, is 6,500 nucleotide bases long (6.5 kb). This segment also contains the HS2ST gene, which overlaps with the RanGAP gene. On distorting (*SD*) chromosomes, this region is 12,000 bases (12 kb), almost twice as long. It contains two copies of HS2ST and RanGAP. Furthermore, the copy of RanGAP on the left-hand side is truncated, missing the final 234 amino acids.

in which *Sd* was located. Patricia Powers cloned this entire region as a series of small overlapping fragments. She then compared each fragment from the *SD* chromosome, which carries the mutant gene, with the corresponding fragment from normal chromosomes.

The comparison revealed only a single difference. A particular fragment was about 6,500 nucleotide bases long on the normal chromosome but was almost twice as long—12,000 bases—on the *SD* chromosome. Further analysis revealed the reason for this size difference. A segment of DNA is duplicated on the mutant chromosome.

Since this was the only detectable difference between the normal and the distorting chromosome, we concluded that it contained at least part of the *Sd* gene. But we needed to know whether it contained all of *Sd*.

To find out, Janna McLean and Cynthia Merrill injected the DNA fragment we believed to contain the distorter gene into *Drosophila* embryos containing only normal chromosomes. The inserted genes can become incorporated in the DNA of some of these embryos. We predicted that if we actually had the *Sd* gene, that embryos receiving and integrating the inserted DNA would acquire the ability to produce offspring that could cause distortion. This in fact is what happened.

Now that we knew that our inserted DNA fragment contained a gene or genes capable of inducing full distorting ability, we hoped we could identify the *Sd* gene itself and determine its function.

From her analysis, Merrill determined that the normal fragment of 6,500 bases actually contains two overlapping genes. One of these is the *Drosophila* counterpart of a mammalian gene encoding heparan-sulfate-2-sulfotransferase (HS2ST). The second gene encoded the *Drosophila* counterpart of a protein known in yeast and mammals as RanGAP. RanGAP has recently been shown to be an essential component of a complex system that transports proteins and RNA molecules into and out of the cell's nucleus.

We discovered that both the HS2ST and the RanGAP genes are represented twice on the *SD* chromosome, as opposed to just once on the normal counterpart. Both genes appear to be normal on the right hand portion of the duplication, as does the HS2ST gene on the left. But the RanGAP gene on the left is not normal; rather it encodes a mutant RanGAP that lacks the last 234 amino acids.

Because this truncated RanGAP protein was the only substantially altered protein encoded in the *SD* fragment, we concluded that this was the one responsible for the distorting activity. If that were true, we expected to be able to find the truncated protein in the testes of distorting males. Leyla Bayraktaroglu and Ayumi Kusano demonstrated that the truncated protein is indeed found in the testes of distorting males, as is the normal-sized protein. In contrast, normal males produce only the normal-size protein.

To obtain decisive proof that we had the right gene, we once again injected a DNA fragment into normal embryos to create distorting flies. This time, Merrill inserted only the left half of the fragment—the one that contains the truncated RanGAP gene. (Since this gene overlaps with the HS2ST gene, it is impossible to insert RanGAP alone. Both genes were inserted together, but HS2ST was disabled and rendered nonfunctional. Only the truncated RanGAP protein could be produced from this fragment.)

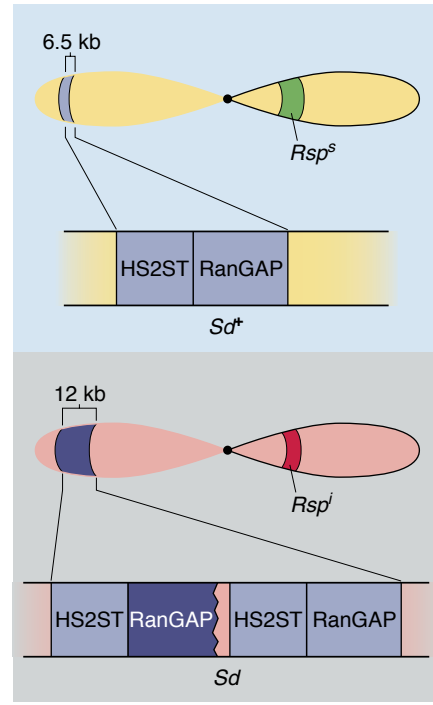

Figure 6. Embryos containing only *Sd*⁺ genes can be transformed to produce flies with distorting activity. Investigators insert a segment of DNA containing the mutant RanGAP gene into embryos with two copies of the *Sd*⁺ gene. The fragment also contains a copy of the HS2ST gene, which overlaps with the RanGAP gene. However, the HS2ST gene has been engineered to render it inactive. Some of the injected embryos will give rise to adult flies that carry the mutant RanGAP gene incorporated into their gametes. After mating these flies to the appropriate tester strain, they produce embryos that carry the mutant RanGAP gene along with an *Rsp*ˢ-bearing target chromosome. The transformed male embryos give rise to adult flies with distorting activity. This experiment demonstrates that mutant RanGAP causes distortion.

The results from this experiment were unequivocal. Flies that received the engineered DNA fragment acquired the ability to cause distortion with the same strength as flies carrying a native *SD* chromosome. Therefore, we concluded that the truncated RanGAP is indeed the functional *Sd* product.

Traffic Jam

As this was the first time that the molecular defect in any meiotic-drive system had been identified, it represented a major step forward. Now that we know that *Sd* encodes an altered RanGAP protein and that RanGAP is important for molecular trafficking across the nuclear membrane, we can start to speculate on possible scenarios for segregation distortion.

We know that chromosome condensation is necessary for spermatids to mature into viable sperm and that this step fails in distorting males when a sensitive *Responder* is present in spermatid nuclei. Various sperm-specific chromosomal proteins are required to bring about chromosome condensation. The messenger RNAs encoding these proteins must be exported from the nucleus to the cytoplasm where the proteins are manufactured. After their synthesis, the proteins must then be imported into the nucleus. Thus, we can readily imagine how a perturbation in nuclear transport could result in failed chromosome condensation by affecting the production or nuclear abundance of these proteins. Because this extreme compaction of chromosomes happens exclusively during sperm development, this probably explains why sperm but not eggs are affected by *Sd*.

Our current studies are aimed at trying to unravel how the truncated RanGAP interferes with nuclear transport. Kusano, in my laboratory, has demonstrated that the mutant RanGAP still retains its normal biochemical activity. However, for various reasons we suspect that the truncated RanGAP could be mislocalized within the cell. This is important because the mechanism of nuclear transport is critically dependent on the normal cytoplasmic localization of RanGAP activity. Nuclear transport would be disrupted if RanGAP were within the nucleus. Merrill has obtained some tantalizing preliminary evidence indicating that the truncated RanGAP is indeed mislocalized to the nucleus

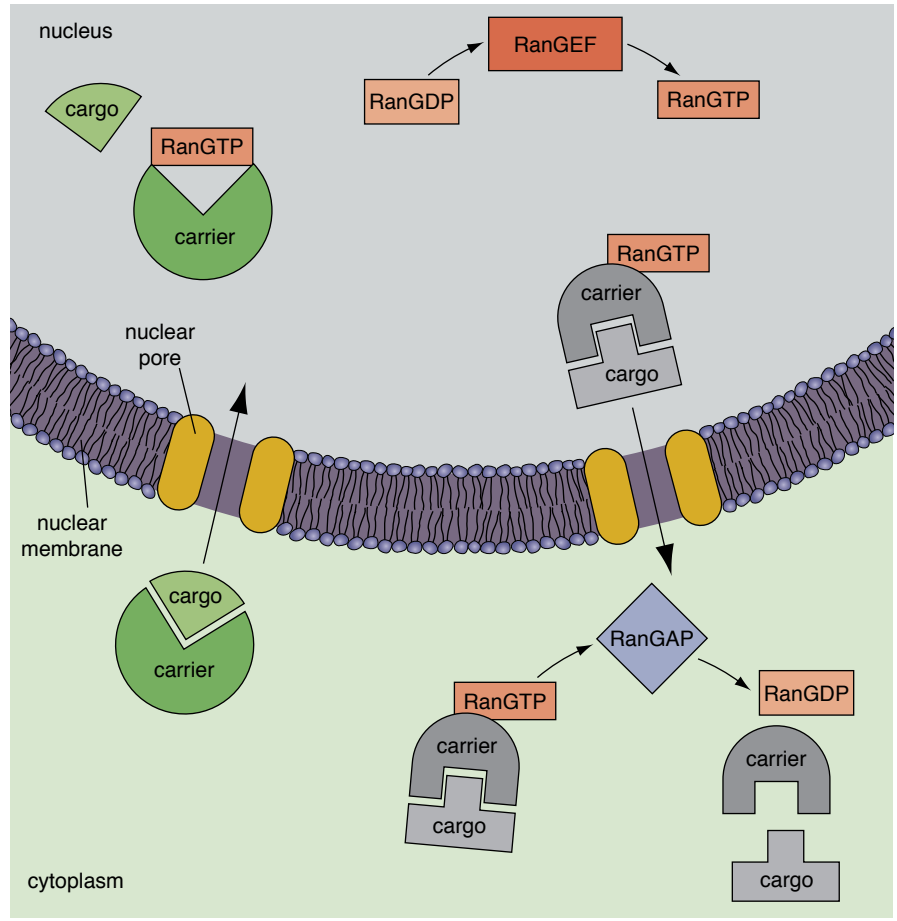

Figure 7. RanGAP protein *(lavender)* has recently been shown to be an essential component of a complex system that transports proteins and RNA molecules into and out of the cell's nucleus. RanGAP is normally found in the cytoplasm, where it helps to convert RanGTP into RanGDP. This conversion brings about the liberation in the cell's cytoplasm of cargo from carrier proteins exported from the nucleus. The reverse reaction, the conversion of RanGDP to RanGTP and the subsequent dissociation in the nucleus of cargo and carrier imported from the cytoplasm, is carried out by RanGEF. The proper localization and concentrations of all of these components are crucial for the smooth transport of molecules across the nuclear membrane.

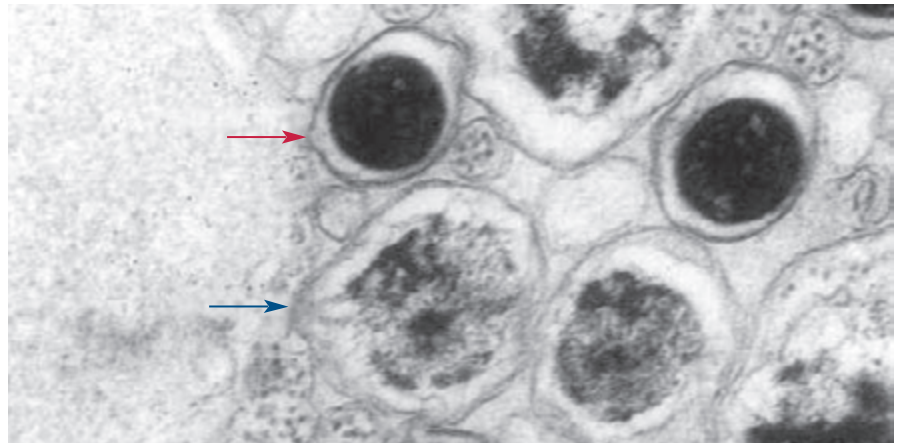

Figure 8. In distorting male flies, chromosomes bearing a *Responder-sensitive* region remain diffuse *(blue arrow)* in the nuclei of spermatids (immature sperm cells). In contrast, chromosomes in spermatids bearing an insensitive *Responder* take on their normal, highly condensed shape within the very compacted nucleus *(red arrow)*. The failure of *Responder-sensitive* chromosomes to condense leads to subsequent defects in sperm maturation with the consequence that these chromosomes are not passed on to the next generation. The inability of chromosomes to condense properly may be related to defects in nuclear transport owing to the presence of mutant RanGAP protein. (Micrograph courtesy of Kiyoteru T. Tokuyasu, University of California, San Diego.)

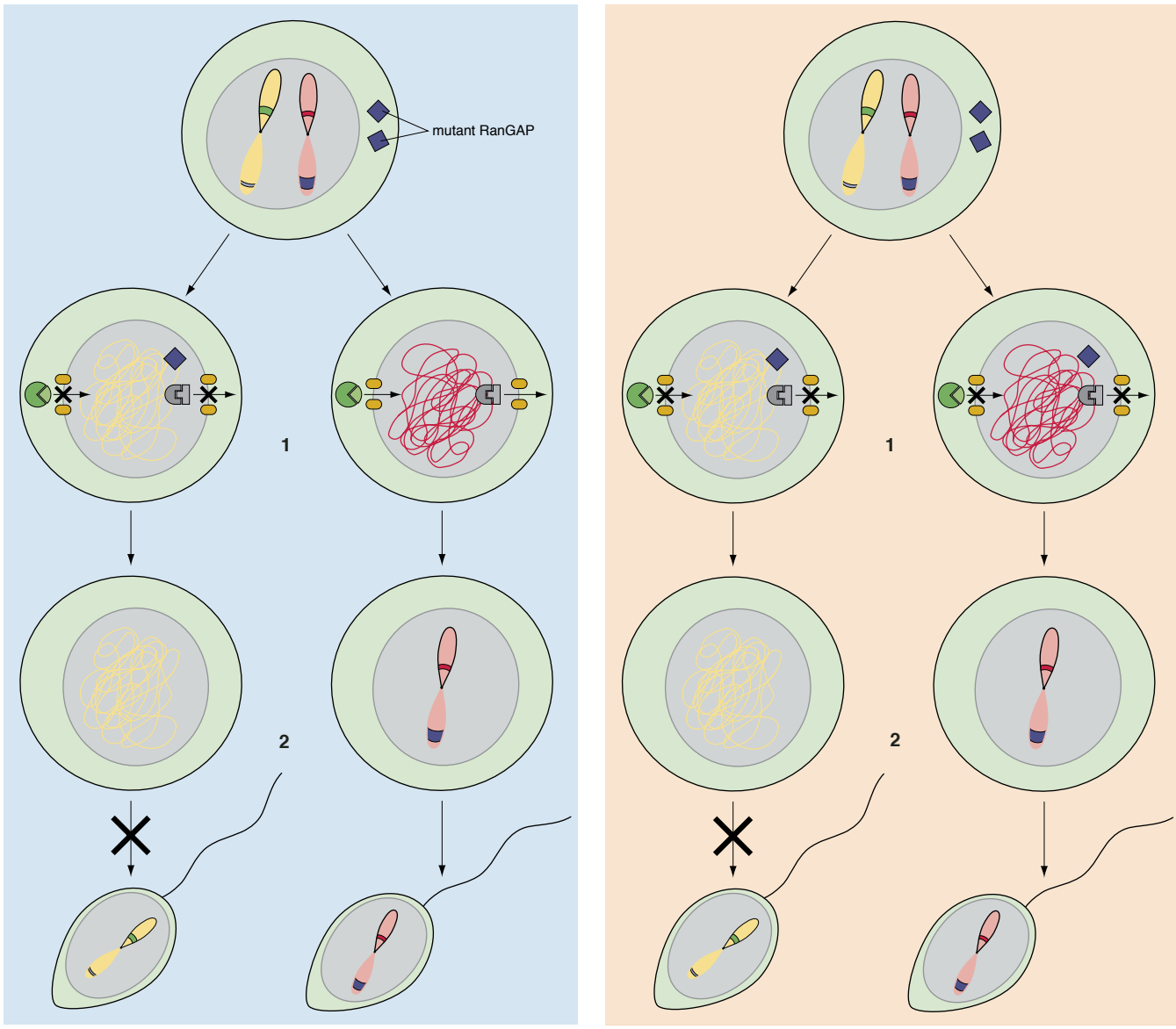

Figure 9. Mutant RanGAP may cause the preferential dysfunction of sensitive spermatids to produce distorted transmission ratios in one of two ways. Truncated RanGAP may be mislocalized to the nucleus only in spermatids containing chromosomes bearing *Rsp*^{s} or *Rsp*^{ss} *(step 1, left panel)*, which disrupts transport, chromosome condensation and maturation of these spermatids *(step 2, left panel)*. Alternatively, truncated RanGAP may become mislocalized in both *Rsp*^{s} and *Rsp*^{i} nuclei and perturb nuclear transport to some extent in both classes of spermatids *(step 1, right panel)*. But spermatids containing *Rsp*^{s}- or *Rsp*^{ss}-bearing chromosomes might be more susceptible to a defect in nuclear transport *(step 2, right panel)* because they contain many more copies of a particular DNA sequence than do *Rsp*^{i}-containing spermatids. These sequences could preferentially bind to the proteins that facilitate chromosome condensation. If the amount of these proteins is limited because of a defect in nuclear transport, there may not be enough to condense the rest of the chromosomes inside the nucleus.

during some stages of sperm development. These results need to be confirmed, and additional experiments are required to determine whether this is what is ultimately responsible for the failed chromosome condensation that occurs in dysfunctional sperm. Experiments to address these issues are under way.

What is more difficult to understand is why in a distorting male, only those spermatids that receive a *Rsp*^{s}- or *Rsp*^{ss}-bearing chromosome are affected by *Sd*. Why do the *Rsp*^{i}-bearing spermatids still develop normally? One possibility is that, for some reason, the truncated RanGAP is mislocalized to the nucleus only in spermatids containing *Rsp*^{s} or *Rsp*^{ss}.

Another possibility is that the spermatids containing *Rsp*^{s}- or *Rsp*^{ss}-bearing chromosomes might be more susceptible to a defect in nuclear transport because they contain many more copies of a particular DNA sequence than do *Rsp*^{i}-containing spermatids. These sequences could preferentially bind to the proteins that facilitate chromosome condensation. If the amount of these proteins is limited owing to a defect in nuclear transport, there may not be enough to condense the rest of the chromosomes inside the nucleus.

Of course, much more work is needed to test these ideas. Segregation distortion has been a puzzle for more than 40 years, and it is probably too much to expect that it will fully give up its remaining secrets any time soon. Nevertheless, for the first time we have been able to identify the underlying molecular defect in a meiotic-drive system.

This advance has offered us an entirely new perspective on segregation distortion, enabling us to frame specific questions and pointing us in the direction of further investigations. It is exciting and satisfying that we have been able to establish a link between *SD* and nuclear transport, a process of fundamental biological importance and currently one of the most vigorously studied areas of cell biology. Undoubtedly, efforts to elucidate the mechanisms of distortion at the cellular level will benefit from the studies of nuclear transport in other experimental systems. Conversely, future studies of *SD* should not only resolve the remaining questions about its mechanism, but may also offer novel insights into the important process of nuclear transport as well.

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