

# Mechanisms of Nucleolar Dominance in Animals and Plants

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In interspecific hybrids, it is often observed that the ribosomal genes of one species are transcriptionally dominant over the ribosomal genes of the other species. This phenomenon has been called “nucleolar dominance” and has been reported in such diverse organisms as frogs (*Xenopus*), *Drosophila*, many genera of plants, and mammalian somatic cell hybrids. Recent advances in our knowledge of the structure of ribosomal genes and their transcription machinery have led to proposals that at least two different molecular mechanisms can operate to cause nucleolar dominance and that the relative contribution of each mechanism is different for different types of crosses. One proposed mechanism involves competition between ribosomal genes which possess unequal numbers of enhancer elements. This mechanism can be abbreviated as the “enhancer imbalance mechanism.” The second proposed mechanism involves the fact that the ribosomal gene (RNA polymerase I) transcription machinery evolves more rapidly between species than does the machinery for the other two classes of polymerase. This leads to dominance effects based on the apparent inability of a key transcription factor from one species to recognize the ribosomal gene promoter of the other species. This mechanism will be referred to as the “species-specific factor mechanism.” The purpose of this review is to briefly summarize the evidence for these two molecular mechanisms and then to examine each of the known types of nucleolar dominance to assess how well the proposed mechanisms can account for each case.

## EVIDENCE FOR ENHANCER ELEMENTS IN RIBOSOMAL GENES

The evidence for enhancers affecting ribosomal gene transcription comes primarily from work on the frog, *Xenopus laevis*. It was initially observed that sequences in the nontranscribed spacer could influence transcription from the gene promoter upon injection of cloned genes into either oocytes (1) or into developing embryos (2). Subsequently, it was demonstrated that the elements responsible for this effect are the 60/81-bp repetitive elements that occur in variable numbers in different spacers (3). The 60/81-bp elements exert their influence in either orientation, at a distance of several kilobases from the gene promoter and even when inserted within the transcribed region of the gene (4, and P. Labhart, unpublished observations). Because of these characteristics, they have been called “enhancers” in analogy with RNA polymerase II enhancers (5).

Within each 60/81-bp repeat in the spacer is a core element of ~42bp which shares 90% homology with a 42-bp domain within the gene promoter itself (1, 6, 7). The 42-bp domain within the gene promoter is nearly coincident with a protein-binding domain as defined by DNaseI footprinting (8). In the spacers of a related species, *Xenopus borealis*, complete 60/81-bp repeats are absent but several copies of the 42-bp core element are present (9). These observations suggest that it is the 42-bp core which is responsible for the enhancer effect. The mechanism by which the enhancers exert their influence on the gene promoter is not known. However, the sequence homology between the enhancers and the promoter, as well as the fact that under certain conditions the enhancers appear to compete with the promoter for the same factor (4), suggests that the enhancers may act as an entry site for a factor involved in promoter activation. (The evidence concerning possible mechanisms of ribosomal gene enhancer function has been reviewed elsewhere [10]). Regardless of the precise mechanism by which enhancers act, all available evidence suggests that a ribosomal gene promoter adjacent to numerous enhancers has a strong advantage over a promoter adjacent to few enhancers. In reconstruction experiments, promoters adjacent to varying numbers of enhancers have been injected in competition into both oocytes and embryos and, in general, the promoter with the most enhancers is transcriptionally dominant (11).

Are ribosomal gene enhancers present in organisms other than *Xenopus*? Two reported attempts to detect any influence of the spacer on ribosomal gene transcription in mammalian species have been negative (12, 13). Other experiments, however, suggest that a repetitive region upstream of the mouse ribosomal gene promoter may have enhancer activity. In transient expression assays a 2-kb *SalI* fragment (that contains multiple copies of a 140-bp repeating element) stimulates transcription (several-fold when present in either orientation) (B. Sollner-Webb, personal communication). The spacers of some species of plants contain variable length blocks of repetitive elements. (The best studied example is the genus *Triticum* [14], as discussed below). Indirect evidence from nucleolar dominance studies suggests that these repetitive elements may be acting as enhancers similar in function to those present in *Xenopus*. Accumulating evidence also suggests that yeast ribosomal genes may contain an enhancer element in each repeating unit. Each repeat contains a 192-bp fragment located just beyond the termination site of the

ribosomal precursor gene (the so-called E-H fragment). The activity of the E-H fragment is strongly dependent upon the sequences which surround it. But, in the correct surroundings, it functions in both orientations, on either side of the gene, and at a distance of at least 2 kb from the site of transcription initiation (15, E. Elion and J. Warner, personal communication). Whether the yeast E-H fragment acts in the same manner as do the *Xenopus* 60/81-bp repeats is still unresolved. The E-H fragment acts in *cis* to stimulate transcription from the adjacent gene at least 10-fold. However, multiple copies of the E-H fragment appear to be inhibitory.

These initial observations raise the possibility that enhancer elements will turn out to be of widespread occurrence among ribosomal genes of many species.

#### EVIDENCE FOR SPECIES-SPECIFIC TRANSCRIPTION FACTORS

As far as is known, RNA polymerase I transcribes only the genes for the large ribosomal RNA precursor (and in some cases, the intervening spacer sequences [16, 17]) and thus interacts with a very limited set of DNA sequences. This is apparently the explanation for the fact that some component of the polymerase I machinery (as well as the promoter sequence itself) is free to evolve rapidly between species. For example, little or no cross-reaction is seen with *in vitro* transcription systems for ribosomal genes between mouse and human (18-21) or between *Drosophila virilis* and *D. melanogaster* (22). In at least one case the species divergence is nonreciprocal. The *X. laevis* ribosomal gene promoter, for instance, appears to work as well as the *X. borealis* promoter does when tested by injection into *X. borealis* oocytes. The *X. borealis* promoter, however, works very poorly in *X. laevis* oocytes (11). For mammals there is good evidence that the species specificity resides in a single transcription factor that changes from species to species. Several laboratories have partially purified a factor which binds tightly to phosphocellulose and which can confer the ability to recognize its own species' promoter when added to an extract from another species (19, 20). This factor has been extensively purified from human cells, and antibodies directed against it stain the nucleolus exclusively (23).

These observations suggest that in crosses between distantly related species, where the polymerase I transcription machinery has evolved apart, the ability of either set of ribosomal genes to be transcribed will depend heavily upon whether or not the appropriate transcription factor is also expressed. In crosses between closely related species, where there is good cross-reaction between the polymerase I promoters and transcription factors, more subtle concerns (such as relative number of enhancers present in each gene set) are likely to determine whether a given gene is transcribed or not.

#### NUCLEOLAR DOMINANCE IN FROGS

Nucleolar dominance in frogs was first described by Blackler and Gecking (24; see also 25) in crosses between *X. laevis* and *X. borealis*. Both of these species have ~500 copies of the ribosomal genes located at a single nucleolus organizer site in each haploid set of chromosomes (26, 27). In normal diploids, two nucleoli are visible throughout early development. However, in F<sub>1</sub> hybrids only one nucleolus is visible, suggesting that one set of ribosomal genes is repressed. Biochemical

analysis subsequently showed that repression of the *X. borealis* ribosomal genes occurs at the level of transcription and that *X. laevis* transcription is dominant over that of *X. borealis* (28, 29). The transcriptional dominance is not due to a maternal effect since *X. laevis* is dominant regardless of which species supplied the egg or the sperm. The dominance of *X. laevis* ribosomal gene transcription is most striking in the case where an *X. laevis* sperm fertilizes an *X. borealis* egg since *X. laevis* ribosomal DNA is dominant even though the egg supplies all the stored transcription machinery that is used when the ribosomal genes first turn on in early development.

A maternal effect is observed, however, when *X. laevis* animals carrying the anucleolate deletion (which deletes at least 95% of the ribosomal DNA [27, 30]) were mated with normal *X. borealis*. When *X. borealis* supplies the egg in such crosses, no repression is seen and the *X. borealis* genes begin transcription at the time they do in normal embryos, shortly after midblastula. From this result it was inferred that repression of *X. borealis* rDNA probably requires nothing else than the physical presence of *X. laevis* rDNA (28). When *X. laevis* supplies the egg, however, transcription of the *X. borealis* rDNA is considerably delayed until the swimming tadpole stage. Thus, in the absence of the *X. laevis* rDNA, something in the *X. laevis* egg severely delays expression of the *X. borealis* rDNA. It has been proposed that both the enhancer imbalance and the species-specific factor mechanisms are responsible for nucleolar dominance in *Xenopus* (11). Between these two mechanisms a reasonable accounting can be made for all the observed phenomena. When a competing pair of ribosomal genes are injected into either oocytes or cleaving embryos, invariably the gene with the most enhancers is transcriptionally dominant. Since the *X. laevis* genes work well in both *X. laevis* and *X. borealis* transcription machinery and have at least fourfold more enhancers, it is predictable that they are dominant regardless of which species supplies the egg (and the transcription machinery).

*X. laevis* rDNA promoters work well in *X. borealis* machinery but the converse is not true. Thus, in crosses where the *X. laevis* rDNA is deleted and *X. borealis* supplies the egg, the *X. borealis* genes turn on at the normal time at midblastula. When the *X. laevis* rDNA is deleted and *X. laevis* supplies the egg, however, turn-on the *X. borealis* genes is delayed. This delay is very likely due to the inability of the *X. borealis* promoters to interact with the stored *X. laevis* transcription machinery. Presumably by the swimming tadpole stage the paternal *X. borealis* genome has synthesized enough of the *X. borealis* factor so that the *X. borealis* genes can begin transcription.

Dominance of the *X. laevis* rDNA is leaky and, in most crosses, expression of the *X. borealis* rDNA (and the presence of two nucleoli per cell) becomes detectable later in development. Since the enhancer imbalance mechanism is presumed only to function when a key transcription factor is limiting in the cell, this may mean that later in development more of the factor is made and it is no longer limiting. Also, in crosses in which *X. borealis* supplies the sperm, this delayed activation could be influenced in part by synthesis of factors specified by the *X. borealis* genome. Nucleolar dominance has been observed in other interspecific crosses within the genus *Xenopus* (M. Fischberg, personal communication) and one cross has been found where the species are co-dominant (*borealis* × *mulleri*). This is very reminiscent of the dominance hier-

archies described in plants (see below) and is readily explained by the enhancer imbalance mechanism. If all enhancers are of equal strength, a species' position in the hierarchy could be determined simply by counting its enhancers. Any two species with the same number would be co-dominant. At present, there is insufficient data available to test this prediction.

## NUCLEOLAR DOMINANCE IN PLANTS

Nucleolar dominance was first described 50 years ago by Navashin (31) who was working with the genus *Crepis*. He noted that the chromosome sets of any particular *Crepis* species invariably contained a pair of large chromosomes, the so-called D-chromosomes, that exhibited a prominent secondary constriction during metaphase. When certain species were crossed, however, the D chromosomes of only one parent would form a secondary constriction in the hybrid. Heitz (32), among others, had shown that such secondary constrictions are the site at which the nucleolus forms during interphase and that constrictions only form when nucleoli are present. McClintock (33) reviewed Navashin's data and predicted that the nucleolus organizers of various *Crepis* species could be ranked in an internally consistent dominance hierarchy based on their ability to suppress nucleolar formation by other organizers or to be suppressed themselves. This prediction was verified by Wallace and Langridge (34) who performed additional crosses to test the dominance hypothesis. These authors proposed that dominance is due to an effect of one organizer on the other and they summarized the basic features of nucleolar dominance as recognized at that time as follows: (a) there is no maternal effect, i.e., the same species is dominant regardless of whether it supplies the sperm or the egg, and (b) the suppressed nucleolus organizer is not irreversibly damaged. It can be recovered in apparently unaltered form by appropriate backcrosses. The reversibility of suppression is seen most clearly during meiosis in the hybrids when haploid spore nuclei form. The suppressed nucleolar organizers activate and form a nucleolus as soon as they are separated from the dominant organizers by a nuclear membrane.

Similar observations have been made subsequently on a variety of plant genera including *Salix* (35), *Ribes* (36), *Solanum* (37), *Hordeum* (38), and *Triticum* (39–42). The ribosomal genes of *Triticum* have been cloned and sequencing has revealed that each spacer contains a large block of repetitive elements that can contain varying numbers of repeats (14). *Triticum* normally contains four nucleolus organizers located on four separate chromosomes. By examining different strains that were deleted for different organizer chromosomes, it was determined that the spacers in a given organizer all have the same length repetitive block but that the size of this block varies between organizers. The volume of the nucleolus formed by each organizer was determined as an approximate measure of the number of active ribosomal genes at that particular site. Nucleolar volume was found to correlate well with increasing length of the repetitive spacer block but was not correlated with the number of genes at each organizer. A plausible hypothesis is that the repetitive blocks are competing for some limiting factor and organizers containing larger repetitive blocks have more active genes even though they may have fewer total genes (R. Flavell, personal communication). A related experiment was one in which a strain was constructed that contained a single organizer-bearing chromosome from *Aegilops umbellulata* in a nucleus with

four normal *Triticum* organizers. *A. umbellulata* is closely related to *Triticum* and the rDNA from both plants is very similar. However, the *A. umbellulata* spacers have a repetitive block that is considerably longer than that found in any of the *Triticum* spacers. This long repetitive block may be the reason that the single *umbellulata* organizer is able to turn off all of the *Triticum* organizers (42).

The similarities between nucleolar dominance in *Xenopus* and the nucleolar dominance seen in plants such as *Crepis* and *Triticum* are quite striking. In both frogs and plants dominance hierarchies have been observed, the dominance is generally independent of maternal influences, and the suppressed ribosomal genes are not irreversibly damaged or lost. The fact that dominance in *Triticum* is correlated with a repetitive element in the spacer strongly suggests that plants may also have enhancer elements in their ribosomal genes and that, as in frogs, enhancer imbalance is primarily responsible for nucleolar dominance.

## NUCLEOLAR DOMINANCE IN MOUSE-HUMAN SOMATIC CELL HYBRIDS

When mouse and human somatic cells are fused it is often observed that one species will be the dominant partner in the hybrid. The chromosomes of the dominant partner will be retained while a variable number of chromosomes from the other species will be lost before the karyotype stabilizes (43). If mouse is the dominant partner, then it is also observed that only mouse ribosomal RNA will be transcribed (44–46) even though some or all of the human ribosomal DNA is retained. By choosing the correct cell lines for fusion, it can also be arranged that the human genome will be the dominant partner, human chromosomes will be preferentially retained, and only human ribosomal genes will be expressed (47). When transcription extracts are made from mouse-dominant hybrid cells, the extracts are unable to recognize the human ribosomal gene promoter even though they transcribe mouse ribosomal DNA perfectly well (48, 49). These facts suggest that in these hybrid cells nucleolar dominance is simply due to the loss (or inactivation) of the gene for the species-specific transcription factor. Since either species has the potential to be dominant, it seems unlikely that enhancer imbalance is involved. An obvious prediction is that the suppressed genes could be reactivated by transfecting the hybrid cells with the gene for the appropriate transcription factor.

There are reports that the inactive ribosomal genes in somatic hybrids can also be reactivated either by infection with SV40 (50) or by treatment with phorbol ester (51). If true, this would argue that the gene for the species-specific factor is not lost but only inactivated (at least in some hybrids) and can be turned back on. In at least one reported case, however, attempts to repeat the phorbol ester reactivation failed (48). Whether this failure was due to differences in the particular hybrid cell lines employed or some other cause is not known at present.

## NUCLEOLAR DOMINANCE IN *DROSOPHILA*

Nucleolar dominance has also been reported in crosses between *Drosophila melanogaster* and *D. simulans* (52). In some respects this dominance also resembles that seen in frogs and plants. One species, *D. melanogaster*, is dominant regardless of the direction of the cross, and the suppressed genes are not

irreversibly lost or damaged. The major difference is that in *Drosophila* a second locus (in addition to the nucleolar organizer locus) has been identified that is required for suppression of *simulans* ribosomal gene transcription to occur (53). The second locus is a region of heterochromatin that is proximal to the nucleolar organizer on the *D. melanogaster* Y chromosome. Deletions of this region, which still retain the nucleolar organizer itself, are unable to suppress the *simulans* genes and co-dominance occurs.

It is not yet clear whether nucleolar dominance in *Drosophila* can be explained by some combination of the enhancer imbalance and species-specific factor mechanisms. The *D. melanogaster* spacers have repetitive sequences in them which are related to the sequence of the gene promoter and which might turn out (in analogy with the *Xenopus* case) to have enhancer activity. However, such enhancer activity has yet to be demonstrated in the *melanogaster* ribosomal genes. It is also possible that the second heterochromatic locus in fact codes for a species-specific transcription factor. But, if that were true, it is not clear how the expression of that locus would cause repression of the *simulans* genes. Another possibility is that *Drosophila* has evolved yet a third, and as yet unknown, mechanism for causing nucleolar dominance.

## CONCLUSION

In crosses between *Xenopus* species, direct evidence suggests that nucleolar dominance is caused by an interaction of two distinct mechanisms, enhancer imbalance and species-specific transcription factors. However, enhancer imbalance appears to be the dominant mechanism and is largely responsible for the fact that *laevis* is dominant in ribosomal gene transcription regardless of the direction of the cross. In mouse-human hybrids, the relative contribution of the two mechanisms seems to be reversed—loss of a species-specific transcription factor explains the facts fairly well, and there is no reason as yet to suspect enhancer involvement. In plants, indirect evidence strongly suggests that enhancer imbalance is involved and could account for all the data so far. *Drosophila*, with another locus outside the nucleolar organizer that affects dominance, does not fit neatly into any of the above categories and perhaps has a third (and as yet unknown) mechanism at work.

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