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Big genes and little genes and deadlines for transcription

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Some deadlines come and go, and the tardy are merely late. But some deadlines have a more exacting consequence, in which all tardy effort is futile. Transcription faces such a deadline — if a cell arrives at mitosis before RNA polymerase completes its sometimes lengthy task of transcribing a gene, then the nascent transcript is aborted. Like the mythical Sisyphus, RNA polymerase begins its task again, all to no avail, unless it meets the next mitotic deadline. From work reported last month by Rothe *et al.*[1], it now seems that the rapid mitotic cycles of an early *Drosophila* embryo impose deadlines that cannot be met by larger genes. The timing of these cell cycles is thus a biological 'gene screen' that precludes expression of large genes at early stages.

The synthesis of a transcript is a substantial task. The mammalian RNA polymerase working at its rate of about 3 kilobases (kb) per minute (37 °C) requires roughly 11 hours to traverse the gargantuan (2,000-kb) dystrophin gene. Measurements[2,3] of the lag between initiation at a promoter and transcription of downstream sequences have shown that the *Drosophila* polymerase progresses at about 1.4 kb per minute (25 °C). At this rate, 55 minutes are required for transcription of the *Ultrabithorax* gene, whereas only 2 are needed for the shorter *knirps* gene. Are these times of any significance to the function of the genes in the control of early development?

Tempo

When copied by a queue of polymerases, the spacing between polymerases, not the total length of the gene, governs the rate of production of completed transcripts. So, although the length of a gene governs the lag time in appearance of completed transcripts, at steady state the yield of transcript is not influenced by gene length. But, in life, transcription is seldom a steady-state process. For example, the formation of pattern in the early *Drosophila* embryo is governed by a cascade of transcriptional regulation. It has been suggested that the lag times in the expression of different genes are important to the tempo of this cascade, and that evolution might tailor this parameter by adjusting intron length, and so gene length and transcription time[2,4].

Even when genes are not turning on and off, the staccato processes of the cell cycle disrupt 'steady state' transcription. Nascent *Ultrabithorax* transcripts are aborted as cells pass through mitosis[3], reappearance of completed transcripts in the next cell cycle being delayed by the 55 minutes required for the task. In cells that initiate transcription of *Ultrabithorax* too late in the cell cycle, the arrival of mitosis prevents completion of transcripts. These results revealed the deadline confronting transcription. Generalization to other transcripts would benefit from a second example, and the principle could be tested by reducing the size of gene that is too large to meet a mitotic deadline. That is what Rothe *et al.* have done.

The deadline for completion of transcripts arrives most swiftly during the rapid early cleavage cycles of the *Drosophila* embryo. These early mitoses are synchronous nuclear divisions in a syncytial cytoplasm. The first ten cycles occur every eight minutes, and of this eight minutes about five are occupied by events of mitosis. During cycles 11, 12, 13 and 14, the interphase period, and time allotted for transcription, lengthens progressively (4, 7, 16 and more than 65

minutes respectively)[5,6]. There is only limited transcription prior to cycle 14 (ref. [7]), and the genes that are known to be expressed during these early cycles are predominantly small. One expects — and the paper by Rothe *et al.* confirms — that a large gene would not meet the transcriptional deadline imposed by these early rapid mitoses.

Rothe *et al.* examined a small gene and a big gene. The *knirps* gene is small (3 kb) and is classified as a gap gene: in its absence, a broad swath (gap) of the embryo is not segmented and fails to develop. The gene is expressed as both RNA and protein in cycle 13. Its expression is confined to a well-defined pattern within the syncytial embryo, and it functions locally as a transcription factor to guide striped expression of the subsequent tier of patterning genes. The *knirps* gene has a big brother, the 23-kb *knirps-related* gene[8]. They differ primarily in the length of their introns. The patterns of transcription and the protein products are similar, but still, *knirps-related* does not provide *knirps* function (ref. [1] and H. Jäckle, personal communication).

Although transcribed in cycle 13, the *knirps-related* RNA product does not leave the nucleus. The RNA product is detected with a 5′ probe but not a 3′ probe, so it is presumably an incomplete and hence nascent transcript. It seems to be aborted at mitosis 13 without ever yielding a completed product. Cytoplasmic transcript finally appears about 20 minutes after mitosis 13, consistent with the expected transcription time of 16 minutes. To test whether this expression delay is due to transcript length, Rothe *et al.* trimmed the 23-kb *knirps-related* gene to 3 kb by removing the introns. This abridged version of *knirps-related* produces cytoplasmic transcripts and a protein product within cycle 13, confirming the adverse effect of gene length in a short cell cycle.

Size

The abridged version of *knirps-related* partially complements a *knirps* mutation, demonstrating that the *knirps-related* product has a modest amount of *knirps* function. It is, however, unclear why the endogenous full-length *knirps-related* gene does not express this function. There are numerous differences between the endogenous gene and the cDNA transgene (note that transgene expression is driven by the 5′ regulatory region of *knirps* and the *knirps* promoter), but one of them — the reduced size of the transgene — points to an explanation that fits the molecular results to a T. As the authors argue, by precluding early expression of completed product, the size of the endogenous gene might prevent expression of *knirps* function.

A gene must be small to be expressed in short cell cycles, but why is *knirps-related* large? Although its involvement in head development occurs later, there is no obvious reason to preclude early expression of *knirps-related*. Because its transcription pattern roughly parallels that of *knirps*, early production of a completed *knirps-related* product should simply provide a redundant *knirps-like* function.

More generally, why should any gene be large, if size compromises function? There are many possible reasons — it might be important to preclude expression of large genes during rapid cell cycles, or delay expression in slower cell cycles, or introduce a temporal lag in a cascade of transcriptional control — but an example of any of them remains to be documented.

References

1. Rothe M, Pehl M, Taubert H, Jäckle H. Nature 1992;359:156–159. [PubMed: 1522901]
2. Thummel CS, Burtis KC, Hogness DS. Cell 1990;61:101–111. [PubMed: 1690603]
3. Shermoen AW, O'Farrell PH. Cell 1991;67:303–310. [PubMed: 1680567]
4. Gubb D. Develop Genet 1986;7:119–131.

5. Foe VE, Alberts B. J Cell Sci 1983;61:31–70. [PubMed: 6411748]
6. Foe VE. Development 1989;107:1–22. [PubMed: 2516798]
7. Edgar BA, Schubiger G. Cell 1986;44:871–877. [PubMed: 2420468]
8. Oro AE, et al. Nature 1988;336:493–496. [PubMed: 2848202]