Cell regulation
Putting together pieces of the big puzzle
Editorial overview

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Abbreviation
σ sigma

Readers who spend their leisure hours engaged in the exasperating task of assembling jigsaw puzzles will know that there are several key steps involved. First, you have to make certain that you have got all the puzzle bits and, more importantly, that you are looking at the correct side of each of the pieces. Next, you have to struggle to set up a framework, usually by using the pieces from the edge. Finally and almost always with the help of one or more friends, you have to fill in the remaining details of the different sections of the puzzle. Readers who spend hours trying to understand the regulation of gene expression in microbes and its coupling to environmental signals will know that there are many similarities between this and assembling jigsaw puzzles!

Actually, these are incredibly exciting times for the very lucky individuals who are currently actively engaged in trying to understand the puzzles of the molecular biology of microbial gene expression. First of all, for many of these puzzles, we now have all of the pieces, in the form of complete genome sequences. This means that we can address most questions at the level of the whole genome, rather than by just studying a few arbitrarily selected genes. Additionally, comparison of different genomes provides a new dimension to the appreciation of sequences. It's like being able to look at someone else's related jigsaw while struggling to complete one's own puzzle. Second, we have clever biophysicist friends to help us assemble our puzzle. This is best illustrated by the case of the bacterial RNA polymerases, in which, thanks to the courageous efforts of Seth Darst, Roger Kornberg and their many collaborators, we now have high resolution structures of several enzymes. Moreover, these enzymes have a common overall structure, suggesting that there is indeed something fundamental out there to be discovered. The review by Korzheva and Mustaev (pp 119–125) describes how this information, together with clever chemical crosslinking data, has been exploited to produce a model of the transcription elongation complex of RNA polymerase. Readers who find this review fascinating should immediately also take a look at Friedman and Court's (pp 201–207) review on bacteriophage λ and think about how antitermination functions impinge on the elongation complex. This is likely to be a very fertile area for many research groups in the next couple of years.

One of the frustrations of doing jigsaw puzzles is that the completion of one segment does not ensure the completion of another neighbouring part. Likewise with real life! Although we now have a very nice model for transcription elongation, owing to the structure of the RNA polymerase core enzyme, we still lack a model for initiation because we don't yet have the structure of the RNA polymerase holoenzyme, which contains sigma (σ), the essential subunit for transcription initiation. This is particularly galling because, traditionally, researchers have focused on the initiation step. Thus, the review by Burgess and Anthony (pp 126–131) summarizes our current knowledge about how the RNA polymerase σ factor docks with core RNA polymerase, and what the σ factor then does. This is especially fascinating, as we know that core enzyme uses common determinants to dock with different σ factors, but we don't know what they are! Extra spice is added because, of course, the high resolution structure of the RNA polymerase holoenzyme containing the σ subunit may be obtained at any moment in the near future and also, very soon, the chemists are going to become interested, as the core–σ interface is the perfect target for new antibacterial reagents.

This issue contains several reviews that are concerned with factors that influence transcription initiation. Rojo (pp 145–151) describes recent thoughts about repression mechanisms, and explains how the mechanism of simple promoter occlusion, which we learned about early on for the *lac* repressor, cannot explain many (if not most) cases of repression. In fact, amazingly, it is the in-depth study of regulation in the *E. coli lac* operon that has led us to understand that repressors can function by looping, jamming or oozing, or a panoply of other mechanisms. Interestingly, not all repressors are gene-specific DNA-binding proteins like the *lac* repressor, and several of the reviews in this issue touch upon the regulation of specific genes by the different proteins that shape the bacterial folded chromosome. See, for example, McLeod and Johnson's (pp 152–159) review on Fis.

Other reviews in this issue concern the molecular biology of activation. For example, Xu and Hoover (pp 138–144) review a class of regulatory proteins that bind at some distance from the target promoter. Their report highlights

persuasive recent evidence that many upstream-bound activators do their job by interacting directly with the σ^{54} subunit of RNA polymerase. This makes for exciting enzymology, as it appears that σ^{54} is 'chivvied' into opening the target promoter DNA by the ATPase activity of the upstream-bound activator. In another review, Martin and Rosner (pp 132–137) describe recent progress in the understanding of the AraC family of transcription activators, and they tell us another amazing story. The key point is that these activators all contain two separate DNA-binding modules. Martin and Rosner explain how MarA, Rob and (presumably) the whole AraC family contain two helix-turn-helix DNA binding motifs that bind to two adjacent major grooves in the DNA at target sites. The frustrating thing about this story is that we still don't know how MarA (or any other AraC family activator) actually activates transcription. However, it is clear that we have all the elements in place for completing the puzzle.

Last, but most certainly not least, many of the reviews in this issue address the regulation of life-and-death biological phenomena. For instance, look at the following: the review by Volkert and Landini (pp 178–185) on transcription responses to DNA damage; the review by Bingle and Thomas (pp 194–200) on plasmid survival; the review by Chatterji and Ojha (pp 160–165) on ppGpp and the stringent response; and the review by Withers, Swift and Williams (pp 186–193) on quorum sensing (surely the most consequential molecular microbiology story of the last decade). It is worth noting and remembering that microbes have evolved their regulatory paraphernalia in order to fulfil essential purposes, and not simply to provide interesting playthings for molecular biologists like us. Thus, the most beautiful mechanisms for transcription activation at a distance described by Xu and Hoover (pp 138–144) are directly connected to many of the phenomena discussed by Ramos *et al.* (pp 166–171). Similarly, Hantke (pp 172–177) describes vital regulation by iron and tells us the unusual story of a Krebs cycle enzyme that, as well as doing its job in metabolism, took on an extra job as a redox-triggered regulator. Some years ago, Akira Ishihama estimated that nearly 5% of the *E. coli* genome (i.e. ≈200 genes) encode proteins that regulate transcription initiation at promoters [1]. Whilst we are waiting for each of the 200 gene products to be given 'the treatment', studies such as those described here are going to provide the vital resource for creative understanding of both simple and complex microorganisms.

But how about more exotic microbes (exotic for us, not for nature!)? We now know that Jacques Monod's celebrated remark that "what is true for *E. coli* is true for the elephant" is not true for transcriptional regulation. Thus, microorganisms of similar size and shape (say, *E. coli* and some archea) can turn out to use entirely different strategies to control transcription initiation. The fact that archea have histones, polymerases and factors more closely related to eukaryotes than to bacteria is one of the big (and informative) surprises in the field. There seems to be an evolutionary continuity between apparently distant fields, to the point that archea are becoming the experimental systems of choice to address the complex and intricate mechanistic aspects of eukaryotic transcription. Coming from the other direction, it is clear that relatively simple signal transduction routes, worked out in detail in some simple eukaryotes, reveal interesting principles of importance for both the prokaryote and the eukaryote world. The review by Bell and Jackson (pp 208–213) on transcription in archaea, and that by Sánchez-Martínez and Pérez-Martín (pp 214–221) on *Candida* and *Ustilago* underscore these messages.

What is the challenge now? The reviews in this issue show that we have accumulated a lot of knowledge about a small number of archetypal regulatory systems. It is possible (or even probable) that, so far, we have only just seen the 'tip of the iceberg', when it comes to the appreciation of the diversity of mechanisms that microbes use to control gene expression. For example, we know very little about anaerobes, about many extremophiles, or about nonculturable bacteria, let alone about simple eukaryotic fungi and protista. So now, do we have to explore more new systems, spreading horizontally? Or do we already have enough information to step up into another level of understanding? We live in an age of information overload, with too many genes, too many sequences and too much data that individuals simply cannot handle. Sadly, there is no answer in sight, yet, other than the hope that adequate bioinformatics will develop rapidly. In the meantime, our advice is to stick with it, read this issue, and simply enjoy the science. After all, it's much less frustrating than doing a jigsaw puzzle!

Reference

1. Ishihama A: Adaptation of gene expression in stationary phase bacteria. *Curr Opin Genet Dev* 1997, 7:582-588.