PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Preface

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PREFACE

The central dogma of molecular biology is that DNA makes RNA and RNA makes protein. Thus the genetic information in the DNA is first converted into an RNA molecule and in turn the information in the RNA is used to make a protein which exerts a particular biological function. A central role in this process is evidently played by the process of transcription in which the DNA is converted into an RNA equivalent. This is true both in prokaryotes where the information in this RNA molecule is rapidly translated to produce a protein and in eukaryotes where a number of processes such as RNA splicing and RNA transport must intervene before the initial RNA transcript is in a form which can be translated into protein.

As well as being of fundamental importance, the process of transcription is also the major regulatory point in both prokaryotes and eukaryotes. Thus in bacteria, the production of new proteins in response to environmental stimuli, for example, is controlled primarily by initiating the transcription of new DNA sequences into RNA. These new RNA species are then translated to produce the new proteins required in a particular situation. Similarly, in eukaryotes the stimulation of transcription is responsible both for the production of new proteins in response to stimuli such as hormones and for the tissue specific expression of different proteins by different cell types. Thus, although some examples of post-transcriptional regulatory processes do exist in eukaryotes, in the majority of cases gene regulation is achieved by selecting which genes will be transcribed into RNA in a particular situation with the remaining steps of RNA splicing, RNA transport and translation following more or less automatically.

Hence the process of transcription is vitally important both in itself and as a control point in both prokaryotes and eukaryotes. Although the actual polymerization of ribonucleotides into RNA on a DNA template is achieved by enzymes known as RNA polymerases, these enzymes cannot function in isolation. Rather they require a number of additional factors to produce correct transcription. These factors are known as transcription factors and include both those which are required for the basal process of transcription of all genes, as well as others which are involved in activating or repressing particular genes in specific cell types or in response to specific stimuli.

Transcription factors were the subject of a two day meeting held at the Royal Society on 25 and 26 October 1995. The particular aim of this meeting was to bring together experts in the fields of prokaryotic and eukaryotic transcription factors to identify similarities and differences between these two areas. In particular it was felt that the subject of transcription factors was normally dealt with in separate meetings analysing either prokaryotic or eukaryotic factors. The meeting began therefore with a series of talks aimed at describing the basal transcriptional apparatus consisting of RNA polymerase and associated factors which is essential for the transcription of any genes. Thus C. A. Gross (UCSF) described studies dealing with the prokaryotic RNA polymerase of *E. coli* which is a multisubunit complex. This core complex, which is used for the transcription of all genes in *E. coli* is associated with an additional subunit known as σ with different σ sigma subunits being associated with the core polymerase in different situations. Most interestingly, this σ subunit serves as a bridge between the core polymerase and activating transcription factors which stimulate transcription in particular situations.

Parallels to this situation were evident in the subsequent talk by R. G. Roeder (Rockefeller University, New York) which described the basal transcriptional apparatus in eukaryotes. Thus the RNA polymerase II enzyme which transcribes protein coding genes in eukaryotes is also associated with a number of different transcription factors which are essential for its activity. Many of these such as the TATA binding protein TBP and TFIIB also act as targets for transcriptional activators which stimulate gene expression in particular situations. Thus these factors are both essential for RNA polymerase activity and can be used as targets to stimulate the activity of the polymerase in different situations. As such, it is obviously of particular interest to understand the structure of these core factors and the manner in which

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they interact with DNA. Progress in this area which has led to the crystallisation of a tripartite complex of DNA, TBP and TFIIB was described by S. K. Burley (Rockefeller University, New York).

This first session thus provided an account of the basal transcriptional complex in both prokaryotes and eukaryotes, as well as providing some indication of how the activity of the complex could be stimulated in particular situations. The regulation of activity of this basal complex by other factors is obviously central to allow particular genes to be activated in particular situations or in particular tissues. This topic therefore formed the subject of the next two sessions which were entitled 'Activation and Repression'. The first of these two sessions focused on the eukaryotic situation. The initial talk by R. Tjian (University of California, Berkeley) described a further complexity of the eukaryotic situation. Thus rather than contacting components of the basal transcriptional complex directly, many activating factors do so via intermediary proteins. These coactivators bridge the gap between the activator and the appropriate target component of the basal transcriptional complex. Such factors can also confer template selectivity by interacting with the RNA polymerase complex to determine which genes are actually transcribed. Thus in eukaryotes stimulation of transcription often requires an activating molecule, a coactivator, components of the basal transcriptional complex and RNA polymerase itself.

In this form of regulation, a key role is obviously played by the binding of an activating molecule to a particular DNA sequence within the regulatory region of an individual gene. Thus such binding results in enhanced transcription by stimulating the activity of the basal transcriptional complex. In this way the presence of a particular DNA sequence can confer on a gene the ability to become activated in response to a particular stimulus. This particular aspect was discussed in the talk by D. Rhodes (Laboratory of Molecular Biology, Cambridge) who described structural studies aimed at understanding the manner in which transcription factors interact with particular DNA sequences. Similarly, in the prokaryotic session, S. Busby (University of Birmingham) described the results of studies indicating how the cyclic AMP receptor protein in *E. coli* bound to its specific DNA target sites and then interacted with either the σ factor or other subunits of RNA polymerase to stimulate transcriptional activation.

These studies can thus be fitted into a simple framework in which an activating molecule binds to a particular DNA sequence either after exposure to a specific stimulus or in a particular cell type. This activating molecule then interacts with coactivating factors, components of the basal transcriptional apparatus or components of the RNA polymerase itself to stimulate transcription.

Other talks in the 'Activation and Repression' sessions dealt however with a phenomenon that is being recognized to be of increasing importance, namely the inhibition of transcription by specific factors. Thus such inhibitory factors are able to specifically reduce the rate of transcription of a particular gene either by interfering with the action of positively acting activator factors or by directly interacting with the basal transcriptional complex to reduce its activity. Such transcriptional repression has been recognised in prokaryotic systems for some years ever since the original description of the *lac* repressor. S. E. V. Phillips (University of Leeds) described the DNA recognition properties of two *E. coli* repressor molecules, the *met* and *trp* repressors which bind two distinct but related sets of sequences.

Although these prokaryotic repressors, have a purely inhibitory function, in eukaryotes such repressors are often closely related to activating molecules. Thus D. S. Latchman (University College London) described studies on the Oct-2 family of transcription factors where inhibiting and activating forms of the molecule are generated from the same primary transcript by alternative splicing, as well as on the Brn-3 family of factors where the activating and repressing forms are encoded by different genes but are closely related to one another. At least in the case of Oct-2, such transcriptional repression appears to be produced by direct interaction of the inhibitory factor with the TFIIEβ component of the basal transcriptional complex. Studies described by J. Manley (Columbia University, New York) showed that the *Drosophila*

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transcription factor *eve* also acts as a direct repressor and provided a detailed analysis of its interaction with another component of the basal transcriptional complex, TBP.

It was clear therefore from these talks that transcription can be regulated by both activating and repressing molecules which interact with the core components of the transcriptional apparatus to either increase or decrease their activity. Obviously, if this system is to be used as a means of gene regulation, some mechanism is required to regulate the activity of these activating and inhibiting factors so that they are only active in response to a particular stimulus or in a specific cell type. Thus, for example, an activating factor can itself become activated after a particular stimulus and then stimulate the expression of appropriate genes. Similarly the activation of an inhibitory factor after a specific stimulus will result in a distinct set of genes being repressed following exposure to this stimulus.

The mechanisms by which this is achieved were discussed in the remaining talks at the meeting. Thus J. Errington (University of Oxford) described the results of studies indicating the mechanism by which the prespore-specific sigma factor σ^F is regulated in *B. subtilis* by two other proteins. This regulation allows σ^F to become activated during prespore development in *B. subtilis* and to switch on the genes required for spore development. Interestingly, one of the factors regulating σ^F has a dual function and also appears to be a structural component of the septum which separates the prespore compartment from the remainder of the bacterial cell. This dual function is also found in eukaryotes where the herpes simplex virus virion component VP16 is also a structural component of the virion as well as a transcriptional activator.

Obviously, the regulatory mechanisms required in eukaryotes are considerably more complex than those in prokaryotes. These were discussed in the final section of the meeting on 'Signalling and regulation'. An example of this complexity was described by R. Treisman (ICRF Laboratories, London) who analysed the activation of the c-fos promoter after addition of serum. Such stimulation, involves the binding to the c-fos promoter of a multiprotein complex containing both the serum response factor and ternary complex factor with each of these factors being activated by different signalling pathways. Similarly P. Chambon (Laboratory of Molecular Genetics, Strasbourg) described the structure of nuclear receptor molecules which mediate gene activation in response to steriod hormones. In particular he described co-factors which link these receptors to the basal transcriptional complex allowing them to activate transcription.

As well as having more complex pathways to respond to specific stimuli, eukaryotes also have to regulate gene expression so that different genes are active in different cell types. In this regard P. Sassoni-Corsi (Laboratory of Molecular Genetics, Strasbourg) described the results of studies which indicated that the Crem factor plays a critical role in sperm development as well as in the control of reproductive behaviour by the pineal gland. Such studies are of particular interest, since the Crem factor was originally isolated as a factor whose activity is modulated by cyclic AMP treatment. Hence these studies provide a link between the activation of factors by specific stimuli and their role in tissue specific gene expression.

Ultimately, such tissue specific gene activation must be sufficiently complex to produce all the different cell types required during development of the eukaryotic organism at the correct place and correct time so that a functional organism is produced. This process has been most extensively analysed in the fruit fly *Drosophila* and H. Jäckle (Max Planck Institute, Gottingen) described studies which have identified a series of transcription factors which interact with one another to produce specific spatial patterns of gene expression in the *Drosophila* embryo. Interestingly one of these factors, Krüppel, can have both positive and negative effects on gene expression. The positive effects occur when this factor interacts with the TFIIB component of the basal transcriptional complex whereas the inhibitory effects are dependent upon its interaction with another component of the complex TFIIE β. Thus this factor illustrates how both positive and negative effects can be achieved by interacting with different components of the basal complex.

Overall, therefore, the meeting provided an opportunity for workers in the prokaryotic and

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eukaryotic transcription factor fields to interact with one another. Although the eukaryotic situation is obviously a great deal more complex, a number of common aspects were identified. Overall the meeting illustrated both similarities and differences in the way in which different organisms respond to the problem of transcribing the information in the DNA molecule into its RNA equivalent and regulating this process so that specific genes can be activated or repressed in response to particular stimuli.

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