

Sigma Factors in Gene Expression

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Sigma factors control the promoter selectivity of bacterial RNA polymerase. The synthesis of new sigma factors allows the coordinated activation of discrete sets of genes and thereby contributes to stress responses, motility, endospore formation, and numerous other adaptive responses.

Introduction

RNA polymerase (RNAP) is the enzyme responsible for the accurate copying, or transcription, of DNA into RNA. This is the first step in the process of information transfer leading to the functional expression of the genetic material and, as such, is frequently a target for regulation.

Transcription initiates at discrete sites (promoters) and proceeds without interruption until specific signals (terminators) are encountered. When RNAP encounters a terminator the RNA product is released and RNAP dissociates from the DNA. The length of the RNA product, or transcript, is therefore defined by promoter and terminator sequences. Some transcripts, such as transfer RNA (tRNA) or ribosomal RNA (rRNA), are part of the translation machinery while others serve as messages for protein synthesis on ribosomes (mRNA). Individual mRNA molecules may contain the information for production of a single protein (monocistronic messages) or multiple proteins (polycistronic messages). Every step in the expression of RNA is potentially a target for regulation, including the initiation, elongation and termination reactions.

Subunit Structure of RNA Polymerase

Bacterial RNAP is a large, multisubunit enzyme with an evolutionarily conserved subunit structure. The overall molecular mass of bacterial RNAP approaches 500 kDa. The core enzyme contains four subunits (two α , β , and β') that together account for the majority of the RNAP mass. While core is catalytically active, and can copy DNA into RNA with high accuracy, it is incapable of recognizing promoter sites.

Sigma (σ) is a dissociable subunit of RNAP. When σ is bound to core, the resulting complex, called holoenzyme, can bind with high affinity to promoter sites. The σ subunit is released soon after RNA transcription is initiated and RNAP begins to progress along the DNA template. Thus, core enzyme is responsible for both the elongation and termination phases of the transcription cycle, while the role

of σ is restricted to promoter recognition and transcription initiation.

The Sigma 70 Family, Sigma⁵⁴

Bacterial σ factors vary in size from about 20 to greater than 70 kDa. The σ factors from diverse bacteria are often functionally similar, as was first appreciated when it was discovered that σ factors from one bacterium could function with core enzyme from a distantly related bacterium. Similarly, promoters also have conserved features common to many bacteria and, as a consequence, genes that are transferred from one organism to another are often able to be expressed. Although many bacteria contain multiple σ factors, typically a single σ is responsible for the majority of transcription in the cell and is therefore essential for viability. This is usually referred to as the primary or principal σ factor. Other σ factors that control specialized functions are considered alternative σ factors. In general, each σ factor imparts upon the resulting holoenzyme a distinct promoter selectivity.

The primary sigma factor from *Escherichia coli* has a molecular mass of approximately 70 kDa and is designated σ^{70} . An alternative σ factor that controls nitrogen-regulated genes is 54 kDa and is designated σ^{54} . These two proteins appear to be structurally unrelated, as judged by comparison of their amino acid sequences, and are the prototypes for two large families of σ factors. All primary, and the majority of alternative, σ factors, are members of the σ^{70} family. Alternative σ factors of the σ^{70} family are themselves grouped into several subfamilies. These include a group of σ factors important in spore formation in *Bacillus subtilis* (sporulation subfamily), a group controlling flagellar gene expression in diverse bacteria (motility subfamily), and an evolutionarily diverged group of factors controlling extracytoplasmic functions such as the synthesis of secreted products, ion uptake or efflux, and

Introductory article

Article Contents

- Introduction
- Subunit Structure of RNA Polymerase
- The Sigma 70 Family, Sigma⁵⁴
- Domain Structure of Sigma Factors
- Promoter Structure and Sigma Factors
- Sigma Substitution in Response to Environmental Cues or for Specialized Functions
- Regulation of Sigma Factor Activity or Presence
- Sigma Substitution and Developmental Gene Regulation
- Sigma as a Contact Site for Positive Regulators

various stress responses (ECF subfamily). The σ^{54} family is also widely represented in many different bacteria and controls a variety of functions including nitrogen metabolism, degradative enzyme synthesis and flagellar genes.

The nomenclature for σ factors is often a source of confusion. In early studies, it was common to refer to newly identified σ factors with a superscript indicating their apparent molecular mass. However, this system became cumbersome as more and more σ factors were identified with similar molecular masses. Moreover, molecular masses as judged from gel electrophoresis experiments are often inaccurate. Two alternative systems have therefore found favour. In one, each σ factor is given a letter designation. In the other, the gene name is used as a superscript. A compilation of σ factors from *E. coli* and *B. subtilis* is provided in **Table 1**. It is unfortunate that it has not yet been possible to assign a consistent set of letter designations to those σ factors with similar functions in these two well-studied organisms.

Domain Structure of Sigma Factors

Bacterial σ factors have at least four distinct biochemical functions. First, they are determinants of promoter sequence recognition and interact closely with the promoter DNA. In the case of the σ^{70} family, this involves contacts between σ and both the -35 and -10 promoter elements, so named to indicate their position relative to the

start point of transcription. In the σ^{54} family, the key elements are located at -12 and -24 . Second, all σ factors must recognize and bind to the core RNAP to allow the assembly of holoenzyme. Since only one σ factor can bind to core at a time, it seems likely that σ factors use a similar binding surface for this interaction. Third, σ factors allow RNAP to associate tightly and specifically with the short region of single-stranded DNA (ssDNA) generated during the promoter melting process. Typically, 12 or so base pairs of DNA need to be strand-separated to allow for the template-directed synthesis of RNA, and formation of this transcription 'bubble' requires σ . Fourth, σ factors provide a contact site for some activator proteins.

In order to define the amino acids within σ factors that contribute to these various biochemical activities, researchers have pursued three main strategies. First, the amino acid sequences of σ factors have been compared to identify those amino acids that are highly conserved throughout evolution and therefore likely to be critical for function. Second, genetic studies have investigated the consequences of mutations in σ factors on core-binding, promoter recognition, DNA melting, and interactions with activators. Third, biochemical approaches (such as covalent crosslinking and footprinting) have allowed specific protein-protein and protein-DNA contacts to be identified.

Members of the σ^{70} family are generally found to have four defined regions of high amino acid sequence conservation separated by less conserved regions (**Figure 1**). The amino-terminal region (region 1) acts as

Table 1 σ Factors in *Escherichia coli* and *Bacillus subtilis*

Organism	σ	Gene	Function
<i>E. coli</i>	σ^{70} (σ^D)	<i>rpoD</i>	Housekeeping genes
	σ^H (σ^{32})	<i>rpoH</i>	Heat shock
	σ^E (σ^{24})	<i>rpoE</i>	Extreme heat shock, periplasmic stress (ECF)
	σ^F (σ^{28})	<i>fliA</i>	Flagellar-based motility
	σ^S (σ^{38})	<i>rpoS</i>	Stationary phase adaptations
	σ^N (σ^{54})	<i>rpoN</i> , <i>glnF</i>	Nitrogen-regulated genes
	σ^{fecI}	<i>fecI</i>	Ferric citrate uptake (ECF)
<i>B. subtilis</i>	σ^A	<i>sigA</i>	Housekeeping genes
	σ^B	<i>sigB</i>	General stress response
	σ^D , σ^{28}	<i>sigD</i>	Flagellar-based motility, autolysins
	σ^E	<i>sigE</i> (<i>spoIIGB</i>)	Sporulation, early mother cell
	σ^F	<i>sigF</i> (<i>spoIIAC</i>)	Sporulation, early forespore
	σ^G	<i>sigG</i> (<i>spoIIIG</i>)	Sporulation, late forespore
	σ^H	<i>sigH</i> (<i>spo0H</i>)	Competence and early sporulation
	σ^K	<i>sigK</i>	Sporulation, late mother cell
	σ^L	<i>sigL</i>	Degradative enzymes
	σ^{ykoz}	<i>ykoZ</i>	Unknown
ECF σ s	<i>sigV</i> , <i>sigW</i> , <i>sigX</i> , <i>sigY</i> , <i>sigZ</i> , <i>yhdM</i> , <i>ylaC</i>	Unknown, some control functions related to membrane and cell wall integrity	

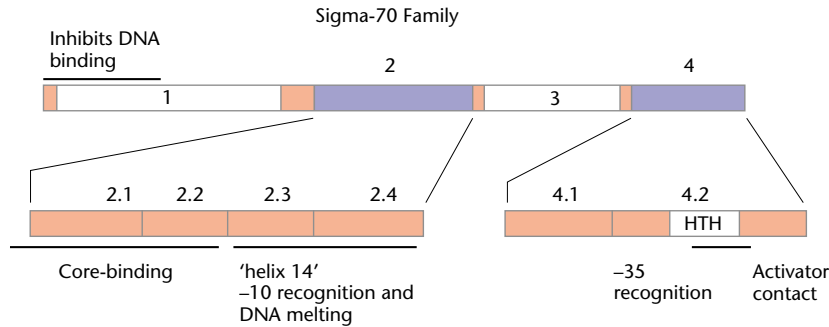


Figure 1 Generic structure–function map for members of the σ^{70} family. The protein sequence is represented as a bar from the amino-terminus (left) to the carboxyl-terminus (right). The amino acid sequence is divided into four conserved regions. Regions 2 and 4 (blue) contain the key regions implicated in core-binding and promoter recognition and melting. Recognition of the -35 promoter element is mediated by a helix–turn–helix (HTH) unit in region 4 and amino acids from this region may also provide a contact point for some activator proteins. Amino acids important for both -10 region recognition and promoter melting are on an α helix (helix 14) spanning regions 2.3 and 2.4.

an allosteric regulator of σ factor function. When σ is free in solution, region 1 appears to mask the DNA-binding domains and thereby prevents association with DNA. When σ binds to core enzyme, region 1 changes conformation so that the DNA-binding surfaces of σ are now exposed. Region 1 may also play a role in subsequent conformational changes during the process of transcript initiation. Region 1 is not essential for σ factor function and, in fact, is not present on many alternative σ factors. In several cases, these alternative σ factors can now recognize and bind to promoter DNA, albeit weakly, even in the absence of the core RNAP.

The two most highly conserved domains of σ^{70} family members correspond to the central conserved region 2 and the carboxyl-terminal region 4. These domains are separated by less conserved, and sometimes absent, region 3. Treatment of σ factors with proteases demonstrates that regions 2 and 4 are independently folded protein structures separated by a protease-sensitive linker region that therefore correspond to folded ‘domains’. The two domains of σ reflect the split nature of bacterial promoters. Region 2, which for convenience has been divided into four subregions, is responsible for recognition and melting of the -10 element and contains key determinants for binding of σ to core RNAP (Figure 1). Region 4 recognizes, and is positioned near, the -35 promoter element with one surface available for interaction with transcription activator proteins bound to adjacent upstream DNA sites.

Similar molecular genetic analyses have been used to define important regions within the σ^{54} family proteins. These proteins are apparently unrelated to the σ^{70} family and have a distinctly different set of conserved regions and domains that, nevertheless, mediate many of the same characteristic σ factor functions. For example, regions important for promoter recognition, promoter melting and activator contact have all been identified.

Promoter Structure and Sigma Factors

Bacterial promoters were originally defined as those sites allowing RNAP to initiate transcription. As technology developed allowing rapid determination of DNA sequences, it became clear that many promoters contained similar sequences positioned near -10 and -35 relative to the start point of transcription. For example, a typical σ^{70} promoter has a sequence similar to TTGACA near -35 and TATAAT near -10 with a separation (spacer) of 17 base pairs (Figure 2). These are average (consensus) sequences and most promoters match this sequence at between 6 and 10 of the 12 indicated positions. In general, the more closely a given promoter matches the consensus, the greater the likelihood that it is a highly active, or strong, promoter in the cell. Those promoters that are recognized by alternative σ factors are characterized by their own consensus sequences, which are often quite distinct from that for σ^{70} indicated above. For example, promoters recognized by σ factors of the motility subfamily often have -10 elements similar to GCCGATAT, rather than TATAAT.

Although it is clear that the most easily identified features of promoters are the conserved consensus elements located near -35 and -10 , it is important to realize that bacterial RNAP is a large enzyme and contacts DNA over an extended region. At a typical promoter site, RNAP will bind to DNA from near -60 to near $+20$ relative to the transcription start point. Furthermore, it is likely that this 80 bp region of DNA is wrapped around the surface of the RNAP contacting each of the individual subunits of core as well as the σ factor.

Recent years have seen tremendous advances in our understanding of the complex interactions between RNAP and promoter DNA and have defined several additional features of this extended region that affect promoter activity. For example, the region between -40 and -60 often interacts with the carboxyl-terminal portion of one or

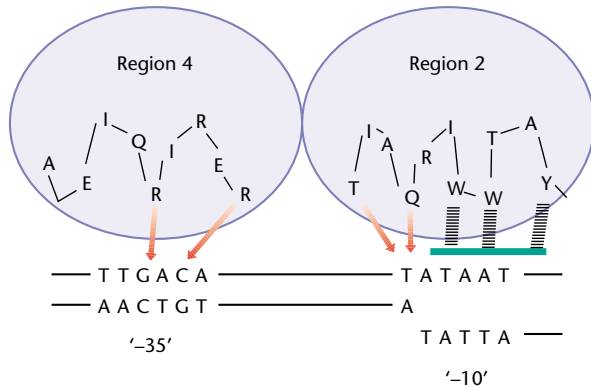


Figure 2 A close-up view of interactions between *E. coli* σ^{70} and a consensus promoter element. The σ factor has two domains corresponding roughly to regions 2 and 4. Region 2 interacts with the -10 element. Conserved threonine (T) and glutamine (Q) residues are implicated in recognition of the start site distal thymine (T in the DNA). An adjacent cluster of aromatic amino acid side-chains (two tryptophan, W, and a tyrosine, Y) provide hydrophobic and stacking interactions (stippled bars) with the ssDNA formed during melting of the promoter DNA. Recognition of the -35 element by region 4 involves, in part, specific amino acid side-chain contacts from two arginine (R) residues with the edges of the base pairs.

both of the two α subunits of RNAP. When present, this upstream promoter (UP) element can increase the rate of RNAP binding and thereby increase promoter strength by 100-fold or more. The distance between the two conserved promoter elements also influences promoter strength and may affect the way in which promoter activity responds to DNA supercoiling. In addition, in some promoters (so-called extended -10 promoters) the spacer region contains an additional conserved element just upstream of the -10 consensus. At these sites, the modified -10 consensus element (TG-TATAAT) may make the -35 region less important as a determinant of promoter strength.

Sequences in or near the start point of transcription, and in the early transcribed region, can also affect the ability of RNA to escape from the promoter and initiate an RNA chain. At most promoters it appears that the initiation of a new RNA chain is an inefficient process; short transcripts are often released (aborted) and RNAP must begin anew prior to successfully elongating through the early transcribed region. At other promoters, RNAP may produce a transcript with a repeated sequence that tends to slip relative to the DNA template. The ability of RNAP to successfully overcome these obstacles and enter into the highly stable and processive elongation mode is a newly appreciated facet of regulation that is determined, in large part, by the sequence in this part of the promoter.

The process of promoter recognition is determined by the interactions of σ factor with the conserved consensus elements. Recognition of the -35 element is governed by an alpha-helical region of domain 4 contained within a

helix–turn–helix DNA-binding motif (**Figure 2**). This interaction is likely to be similar, at least superficially, to that of other DNA-binding proteins that use a helix–turn–helix motif. That is, amino acid side-chains project from the exposed recognition helix into the major groove of duplex DNA to establish sequence-specific hydrogen-bonding interactions.

In contrast with -35 region recognition, the ability of σ to contribute to sequence discrimination in the -10 region is complex. The key amino acids implicated in -10 region recognition are also located on the exposed surface of an α helix. In this case, some amino acids may interact with the -10 region as duplex DNA while others may interact with single-stranded DNA (ssDNA) formed during the promoter melting process. Indeed, it is now clear that RNAP can bind tightly to ssDNA and this binding is highly sequence selective: RNA binds to the nontemplate strand of the promoter much more tightly than to the template strand. This has led to a model for σ factor function in promoter recognition and melting in which the -10 recognition helix forms part of an ssDNA binding pocket that functions both to melt the promoter and to recognize portions of the -10 consensus. Remarkably, the presence of -10 -like sequences in the early transcribed region (between $+1$ and $+25$) can even lead to a σ ‘hopping’ phenomenon in which domain 2 of σ can bind to ssDNA exposed on the nontemplate strand by the movement of RNAP away from the promoter. This leads to a slowing of the elongating RNAP (a ‘pause’) and can thereby slow down promoter escape.

Sigma Substitution in Response to Environmental Cues or for Specialized Functions

The replacement of the primary σ factor with alternative σ factors is a powerful means of activating gene expression. The ability of RNAP to be ‘reprogrammed’ by σ substitution was first discovered in biochemical studies of bacteriophage transcription in *B. subtilis*. An infecting bacteriophage can produce a new σ subunit that can redirect RNAP from the host cell to specifically transcribe phage genes. Soon, it was appreciated that this same strategy is responsible for the activation of numerous genes in uninfected cells (see **Table 1**). It is important to realize that σ substitution is not an all-or-none process. Multiple σ factors can coexist in the cell each interacting with a small or large fraction of available RNAP core enzyme. However, in some circumstances a new σ factor may become so dominant as to control the bulk of cellular transcription.

The first alternative σ factors characterized were found in the spore-forming bacterium *B. subtilis*. These proteins

were identified in biochemical studies in which fractions of RNAP were found that had altered promoter selectivity. It is now appreciated that this organism has an unusual abundance of alternative σ factors, many of which participate in spore formation, a process considered in more detail below. Others control groups of coordinately regulated genes (a 'regulon') composed of stationary phase stress genes (σ^B) or genes for flagellar motility (σ^D).

The discovery of alternative σ factors in the other mainstay of bacterial genetics, *E. coli*, followed a different course. In this case, genetic studies identified positive regulatory proteins required for the expression of sets of genes. For example, a gene for a regulator of high temperature protein synthesis (*htpR*) was later found to encode a protein similar in sequence to σ factors. Subsequently, σ factor activity was documented for the corresponding protein. A similar history pertains to the discovery of σ^{54} .

All bacteria for which information is available have one or more alternative σ factors. The actual number varies between species. In *Mycoplasma genitalium*, notable for its very small genome, only two of the 500 or so genes encode σ factors. The *Helicobacter pylori* and *Haemophilus influenzae* genomes encode three and four σ factors, respectively. In contrast, *Mycobacterium tuberculosis* encodes 13 σ factors including ten members of the ECF subfamily.

Regulation of Sigma Factor Activity or Presence

The activity of individual σ factors within the cell is controlled in numerous ways. In many cases, alternative σ factors are only synthesized in response to specific clues or growth phase transitions. This synthesis is frequently controlled at the level of transcription, but in some cases there is translational control. Another regulatory strategy involves the synthesis of alternative σ factors as inactive proproteins that must have an inhibitory leader peptide cleaved in order to become active. Examples include the *B. subtilis* sporulation σ factors, σ^E and σ^K . In each of these examples, the synthesis or processing of a new σ factor is essentially irreversible. Since σ factors act catalytically to facilitate RNA chain initiation, a very small number of active σ factors can lead to the synthesis of multiple mRNAs that, in turn, can each direct the synthesis of multiple protein products. Thus, just as the activation of new σ factors is regulated, it is also important to be able to rapidly inactivate σ factors. Often, σ factors have a short half-life and are rapidly degraded by intracellular proteolysis.

The synthesis or processing of an active σ factor at time of need, followed by rapid turnover, provides a burst of transcription from the targeted genes but is an energetically

expensive strategy. An alternative approach would be to reversibly control σ factor activity by a covalent or noncovalent posttranslational modification. In this manner, transcription could be turned on and off repeatedly. One way in which this can be achieved is through the use of regulatory proteins that prevent or enable σ factor activity only under certain conditions. For example, alternative σ factors may not themselves be sufficient for promoter activation. Rather, the holoenzyme may also require a positive-acting regulatory protein. This strategy has been adopted by several members of the σ^{54} family of proteins, which are generally ineffective in the absence of a positive activator. Another common way in which this is done is through the use of specific anti- σ factors that bind to, and stoichiometrically inactivate, the σ protein. For example, *E. coli* σ^{FecI} is bound in an inactive complex with a membrane-bound anti- σ , FecR, that can sense the presence of ferric citrate in the periplasmic space. When this iron source is present, the σ is released to allow the transcription of the corresponding iron citrate transport machinery. Similar, reversible inactivation of σ factors regulates *B. subtilis* σ^B , σ^D , and σ^F .

The regulation of σ activity by anti- σ factors raises the question of how anti- σ factors can be regulated. Here too, numerous mechanisms have come to light. In some cases, the σ -anti- σ interaction is controlled by a small molecular ligand (e.g. ferric citrate), whereas in other cases the σ -anti- σ interaction is controlled by reversible interaction of the anti- σ with another regulator, an anti-anti- σ factor! In the case of *B. subtilis* σ^B , a cascade of at least four regulatory proteins ultimately controls the activity of a single σ factor.

Regulation of the flagellar σ factors by their cognate anti- σ , known as FlgM, provides a beautiful example of how a structural change in the cell can control σ factor activity. The flagellar σ factors (generically called σ^{28} factors) of *E. coli* and *B. subtilis* control the synthesis of flagellin, the major structural protein for the large extracellular motility appendage, the flagellum. Prior to the successful assembly of the hook and basal body structure, which is required for assembly of the flagellin monomers into the flagellar filament, σ^{28} is held in an inactive complex with FlgM. Once the hook and basal body is assembled, FlgM is a substrate for the export apparatus and is pumped from the cell through the same channel that allows export and assembly of flagellin. Thus, completion of one part of the structure (the hook-basal body) provides a conduit for export of the anti- σ and thereby allows synthesis of the substrate for assembly of the next part of the structure, flagellin. The coupling of morphological changes to σ activation also plays a key role in the σ cascade leading to endospore formation.

Sigma Substitution and Developmental Gene Regulation

The process of development, in which a single progenitor cell type can give rise to differentiated cells of multiple types, is a characteristic of multicellular life. Bacteria, generally being thought of as single-celled organisms, would not seem to be an attractive model for the study of development. However, bacteria, like higher cells, often must choose between alternative cell fates. In the environment, bacteria function as part of complex, multispecies communities of organisms and cell-to-cell signalling, both within and between species, is the rule rather than the exception.

One very well studied example of bacterial development, and one that is largely controlled by alternative σ factors, is the process of endospore formation in *B. subtilis*. Upon encountering nutrient limitation, a single *B. subtilis* cell can divide asymmetrically to give rise to two unequal daughter cells, the larger designated the mother cell and the smaller called the forespore. The mother cell subsequently engulfs the forespore, which then becomes a cell within a cell. Throughout the next several hours, these two cells are in constant communication, exchanging signals necessary for the maturation of the forespore into a mature, heat-resistant endospore that is ultimately released by the lysis of the mother cell. This process involves dramatic changes inside the forespore, including a complete repackaging of the chromosome into a stable but virtually inert state. Meanwhile, the outside of the forespore acquires an altered cell wall and a tough proteinaceous coat synthesized by the mother cell.

The process of sporulation is triggered by activation of a single key transcription factor, Spo0A, that then activates transcription of numerous genes including the first σ factor dedicated to the process of sporulation, σ^F . Although σ^F is synthesized prior to the asymmetric septation that divides the cell into the mother cell and the forespore, σ^F only becomes active in the forespore owing to a compartment-specific release from the inhibitory influence of its cognate anti- σ factor. Once σ^F is activated in the forespore, a σ^F -dependent signal is sent back to the mother cell that leads to the proteolytic processing of active σ^E from an inactive precursor protein. Thus, σ^F acts to direct early transcription in the forespore, while σ^E is the first mother cell-specific σ factor. Once the process of engulfment of the forespore is complete, another signalling event takes place. An unknown signal, dependent on σ^E , triggers the σ^F -dependent transcription of the forespore gene encoding σ^G . The late forespore σ (σ^G) then controls the final stages in the spore maturation process and is required, in a final step of cell–cell signalling, for the maturation of the second mother cell σ factor, σ^K , from an inactive precursor protein.

Analysis of the roles of σ factors in endospore formation provides well-documented examples of alternative σ factors in action, including the use of one σ to control transcription of a later-acting σ (the ‘cascade’ model), anti- σ factors, processing of σ factors from inactive precursors, and cell-to-cell communication.

Sigma as a Contact Site for Positive Regulators

While the production of alternative σ factors may be sufficient to activate new promoter sites, the activity of the primary σ factor is typically regulated by promoter-specific, DNA-binding proteins such as repressors and activators. In addition, some alternative σ factors either require, or are largely dependent on, a positive acting regulator (activator) for their activity. While any protein that blocks access of RNAP to the promoter region can act as a repressor, the activation of transcription is more complex. In order to increase the rate of transcript initiation from a promoter, an activator protein must increase the rate of the slowest step (rate-limiting step) along the initiation pathway. Activator proteins frequently accomplish this task by making specific protein–protein contacts with one or more components of RNAP. While the α subunits are probably the most frequent targets for positive regulators, a favourable interaction between an activator protein and any RNAP subunit, including σ , can activate transcription. One well-characterized example of an activator that contacts σ is the phage lambda cI repressor protein. When bound at the P_{RM} promoter, cI contacts RNAP using, at least in part, a specific aspartic acid residue. Genetic studies have identified a corresponding, oppositely charged, residue (Arg596 from region 4) in *E. coli* σ^{70} as a probable partner for this interaction.

The effect of interactions between activator proteins and RNAP, including σ , are hard to predict. At many promoter sites, the contact appears to increase the ability of RNAP to bind to the promoter site. However, in other cases, it is likely that the protein–protein interaction facilitates, by unknown mechanisms, subsequent steps along the initiation pathway, such as promoter melting or clearance. In the case of σ^{54} -dependent promoters, RNAP can often bind to the promoter site in the absence of the activator but fails to initiate transcription. Thus, in this case, it is almost certainly the DNA melting step that is enabled by the activator protein.

Further Reading

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