Biol 4564/6564 Advanced Genetics

Gene Expression: Prokaryotes

Chapters 17 & 24
• **In negative regulation**, a repressor protein binds to an **operator** to prevent a gene from being expressed.

• **In positive regulation**, a transcription factor is required to bind at the promoter in order to enable RNA polymerase to initiate transcription.
Regulation of Transcription in prokaryotes is a complex and multi-tiered phenomenon.
(a) Lactose absent, repressor active, operon off

(b) Lactose present, repressor inactive, operon on
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(a) Lactose absent, repressor active, operon off

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The *lac* Operon Has a Second Layer of Control: **Catabolite Repression**

A small molecule inducer, cAMP, converts an activator protein, CRP, to a form that binds the promoter and assists RNA polymerase in initiating transcription.
lacZ promoter -loss of consensus: optimal expression NOT maximal expression

-35

T82 T84 G78 A65 C54 a45

-10

T80 A95 T45 A60 a50 T96

Promoter sequence numbering

GC TTTACA CTTTATGCTTCCGGCTCGTATGTTGTGTGGA.....

C CGAAATGTGAAATACGAGGCCCAGGATACAAACACACCT.....

lacZ

lacI
lacZ promoter - loss of consensus: optimal expression NOT maximal expression

-35 -10

- T82 T84 G78 A65 C54 a45  <--- 17 bp ----> T80 A95 T45 A60 a50 T96

Promoter sequence numbering
Promoter Efficiencies Can Be Increased or Decreased by Mutation

- **Down mutations** tend to decrease promoter efficiency, usually decrease conformance to the preferred interactions with the “consensus sequences”, whereas **up mutations** have the opposite effect.

- Mutations in the **–35 sequence** tend to affect **initial binding** of RNA polymerase **holoenzyme**.

- Mutations in the **–10 sequence** tend to affect **binding of the holoenzyme** or the **melting reaction** that converts one of the **closed** complexes to an **open** complex.
Regulation of Transcription in prokaryotes is a complex and multi-tiered phenomenon.
The \textit{lac} Operon Has a Second Layer of Control: \textbf{Catabolite Repression}

A small molecule inducer, cAMP, converts an activator protein, CRP, to a form that binds the promoter and assists RNA polymerase in initiating transcription.

**CRP** Catabolite Repressor Protein

**CAP** Catabolite Activator Protein
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The *lac* Operon Has a Second Layer of Control: Catabolite Repression (as do ALL secondary metabolites in *E. coli*)

A dimer of CAP (sometimes called CRP) is activated by a single molecule of *cyclic AMP* (cAMP).

- cAMP is controlled by the level of glucose in the cell; a low glucose level allows cAMP to be made.

- CAP or CRP interacts with the C-terminal domain of the α subunit of RNA polymerase to activate it.

**FIGURE 27: Glucose reduces CRP activity**
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**FIGURE 27: Glucose reduces CRP activity**
- The *lac* repressor protein binds to the double-stranded DNA sequence of the operator.

- The operator is a **palindromic** sequence of 26 bp.

- Each inverted repeat of the operator binds to the DNA-binding site of one repressor subunit.
FIGURE 13: Lac repressor monomer has several domains


FIGURE 13: Lac repressor monomer has several domains
Different types of mutations occur in different domains of the repressor protein.

- $lacI^d$ (dominant negative; cannot bind to DNA)
- $lacI^s$ (dominant; either cannot bind or cannot respond to inducer)
- $lacI^-$ (recessive; cannot repress)

Mutations identify repressor domains
• Monomers form a dimer by making contacts between core subdomains 1 and 2.

• Dimers can also form a tetramer by interactions between the tetramerization helices.

• **Bipartite nature** of the *lac* repressor

**FIGURE 15:** Repressor is a tetramer of two dimers
• Each dimer in a repressor tetramer can bind an operator, so that the tetramer can bind two operators simultaneously.

• Full repression requires the repressor to bind to an additional operator downstream or upstream as well as to the primary operator at the lacZ promoter.

• Binding of lacI repressor at the operator stimulates binding of RNA polymerase at the promoter but **precludes** transcription.
The Operator Competes with Low-Affinity Sites to Bind Repressor

- The large number of low-affinity sites ensures that all repressor protein is bound to DNA.
- Repressor binds to the operator by moving from a low-affinity site rather than by equilibrating from solution.

FIGURE 24: Repression affects the sites at which repressor is bound on DNA
• Binding of repressor at the operator stimulates binding of RNA polymerase at the promoter but precludes transcription.

• It also opens up the “activator” site for binding of CAP the “Catabolite Activator Protein” to bind……and as soon as lactose is present the system is primed to go!!!

FIGURE 21: Repressor can make a loop in DNA
http://biotech.gsu.edu/4564/Regulatory_models.html
We can combine all activation and repressible activities into four distinct combinations:

- negative inducible,
- negative repressible,
- positive inducible,
- positive repressible.

Induction and repression can be under positive or negative control.
Other Repressible systems....
The *trp* Operon Is a Repressible Operon with Three Transcription Units
We can combine all activation and repressible activities into four distinct combinations:

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Induction and repression can be under positive or negative control.
The global regulatory protein FruR modulates the direction of carbon flow in *Escherichia coli*

Tom M. Ramseyer¹, Stefan Bledig², Valerie Michotey¹, Rita Feghali¹, Milton H. Jr Saier¹.

Article first published online: 27 OCT 2006
DOI: 10.1111/j.1365-2958.1995.tb02339.x

**Summary**

The *Escherichia coli* fructose repressor, FruR, is known to regulate expression of several genes concerned with carbon utilization. Using a previously derived consensus sequence for FruR binding, additional potential operators were identified and tested for FruR binding in DNA band migration retardation assays. Operators in the control regions of operons concerned with carbon metabolism bound FruR, while those in operons not concerned with carbon metabolism did not. *In vivo* assays with transcriptional lacZ fusions showed that FruR controls the expression of FruR operator-containing genes encoding key enzymes of virtually every major pathway of carbon metabolism. Moreover, a *fruR* null mutation altered the rates of utilization of at least 36 carbon sources. In general, oxidation rates for glycolytic substances were enhanced while those for gluconeogenic substances were depressed. Alignment of FruR operators revealed that the consensus sequence for FruR binding is the same for operons that are activated and repressed by FruR and permitted formulation of a revised FruR-binding consensus sequence. The reported observations indicate that FruR modulates the direction of carbon flow by transcriptional activation of genes encoding enzymes concerned with oxidative and gluconeogenic carbon flow and by repression of those concerned with fermentative carbon flow.
FIGURE 4 Model for transcriptional regulation of target genes by the FruR protein. The figure depicts a negatively regulated operon (fruBKA) and a positively regulated operon (pckA). In the absence of an effector molecule (fructose 1-phosphate or fructose 1,6-diphosphate), FruR binds to the operator site(s) (O) in the control region of the target operon. Negatively regulated genes (−) are repressed, whereas positively regulated genes (+) are activated. While the fru operon exhibits two FruR operators, only one is found in the pckA operon. Binding of an effector molecule to the FruR protein causes it to dissociate from the DNA, thereby derepressing or deactivating gene expression. In the pckA operon, two cAMP-CRP-binding sites in addition to the promoter (−35/-10) are indicated.
Glucose

Hxk1 & 2

Gluc 6-P

Fruc 6-P

Fruc 1, 6-P

Fba1

DHAP

Glyceraldehyde 3-P

Tdh3

1, 3-Bisphosphoglycerate

Pgk1

3-P Glycerate

2-P Glycerate

Eno2

P-Enol Pyruvate

Pyruvate

Pdc1

Acetaldehyde

Adh1

Ethanol

NAD^+ NADH_2^+

NADPH_2^+ NADP^+

6-P Gluconate

6-P Gluconolactone

Pentose 5 P
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We can combine all activation and repressible activities into four distinct combinations:

- negative inducible,
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Induction and repression can be under positive or negative control.
Consensus Promoter Sequences

-35

-10

- T82 T84 G78 A65 C54 a45  
  <--- 17 bp --->  T80 A95 T45 A60 a50 T96
Bacterial RNA Polymerase Terminates at Discrete Sites

• There are two classes of terminators: Those recognized solely by RNA polymerase itself without the requirement for any cellular factors are usually referred to as “intrinsic terminators.”

• Others require a cellular protein called rho and are referred to as “rho-dependent terminators.”
Bacterial termination occurs at a discrete site.
• **Intrinsic termination** requires the recognition of a terminator sequence in DNA that codes for a **hairpin** structure in the RNA product.

• The signals for termination lie mostly within sequences that have *already been transcribed* by RNA polymerase, and thus termination relies on scrutiny of the template and/or the RNA product that the polymerase is transcribing.

**FIGURE 28**: An intrinsic terminator has two features
• **read through** – Does occur at *transcription* or translation termination sites when RNA polymerase or the ribosome, respectively, ignores a termination signal because of a mutation of the template or the behaviour of an accessory factor.

• **antitermination** – A mechanism of transcriptional control in which termination is prevented at a specific terminator site, allowing RNA polymerase to read into the genes beyond it.

• **polarity** – The effect of a mutation in one gene influencing the expression (though either transcription or translation) of subsequent genes in the same transcription unit.
Transcriptional Termination Can Also Be a Regulatory Event

1. RNA polymerase transcribes DNA
2. Rho attaches to *rut* site on RNA
3. Rho translocates along RNA
4. RNA polymerase pauses at hairpin and rho catches up
5. Rho unwinds DNA-RNA hybrid
6. Termination: all components released

Rho terminates transcription
How Does Rho Factor Work?

- Rho factor is a hexameric protein that binds to nascent RNA and tracks along the RNA to interact with RNA polymerase and release it from the elongation complex.

- **rut** – An acronym for **rho utilization site**, the sequence of RNA that is recognized by the **rho** termination factor.
• **polarity** – The effect of a mutation in one gene in influencing the expression (at transcription or translation) of subsequent genes in the same transcription unit.

• **antitermination complex** – Proteins that allow RNA polymerase to transcribe through certain terminator sites.

Rho can terminate when a nonsense mutation removes ribosomes
Antitermination Can Be a Regulatory Event
**FIGURE 26.36** The *trp* leader region can exist in alternative base-paired conformations. The center shows the four regions that can base pair. Region 1 is complementary to region 2, which is complementary to region 3, which is complementary to region 4. On the left is the conformation produced when region 1 pairs with region 2 and region 3 pairs with region 4. On the right is the conformation when region 2 pairs with region 3, leaving regions 1 and 4 unpaired.
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**FIGURE 26.37** The alternatives for RNA polymerase at the attenuator depend on the location of the ribosome, which determines whether regions 3 and 4 can pair to form the terminator hairpin.

**FIGURE 26.38** In the presence of tryptophan tRNA, ribosomes translate the leader peptide and are released. This allows hairpin formation, so that RNA polymerase terminates. In the absence of tryptophan tRNA, the ribosome is blocked, the termination hairpin cannot form, and RNA polymerase continues.

paused until a ribosome translates the leader peptide. The polymerase is then released and moves off toward the attenuation site. By the time it arrives there, the secondary structure of the attenuation region has been determined.

**FIGURE 26.38** summarizes the role of Trp-tRNA in controlling expression of the operon.
Consensus Promoter Sequences

\[
\text{Startpoint} \quad \text{Promoter} \quad \text{Terminator}
\]

-35 \text{--} 10 \text{--} 1+1 \text{--} +10

- 35 bp -->

T82 T84 G78 A65 C54 a45 \text{---} 17 bp \text{---} T80 A95 T45 A60 a50 T96
Competition for Sigma Factors Can Regulate Initiation

- The activities of the different sigma factors are regulated by different mechanisms.

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*E. coli* has several sigma factors
Competition for Sigma Factors Can Regulate Initiation

E. coli has several sigma factors: RpoD and RpoS.
Competition for Sigma Factors Can Regulate Initiation

- *E. coli* has several sigma factors, each of which causes RNA polymerase to initiate at a series of discrete promoters defined by specific –35 and –10 sequences.

Sigma controls promoter recognition
Competition for Sigma Factors Can Regulate Initiation

- The activities of the different sigma factors are regulated by different mechanisms.

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\emph{E. coli} has several sigma factors
Competition for Sigma Factors Can Regulate Initiation

- **heat shock response** – A set of genetic loci that is coordinately activated in response to an increase in temperature (and other conditions that might damage/alter normal cellular activity) that may otherwise cause proteins to denature.

  - All organisms have this response.
  - The gene products usually include *chaperones* that act on denatured proteins.
Competition for Sigma Factors Can Regulate Initiation

- *E. coli* has several sigma factors, each of which causes RNA polymerase to initiate at a series of discrete promoters defined by specific –35 and –10 sequences.
A cascade of sigma factors is created when one sigma factor is required to transcribe the gene coding for the next sigma factor.

The early genes of phage SPO1 are transcribed by host RNA polymerase.

One of the early genes codes for a sigma factor that causes RNA polymerase to transcribe the middle genes.

Two of the middle genes code for subunits of a sigma factor that cause RNA polymerase to transcribe the late genes.

Alternative sigmas control phage development.
Sigma Factors May Be Organized into Temporal Cascades

...expression of phage genes, mycobacteriophage PDRPxA

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Alternative sigmas control phage development
Sporulation Is Controlled by Sigma Factors

Sporulation occurs through an ordered series of sigma production ordered events.
Sporulation Is Controlled by Sigma Factors

Sporulation occurs through an ordered series of sigma production ordered events.

- **Vegetative bacterium**
- **DNA replicates**
- **Septum forms**
- **DNA translocates into forespore**
- **Spore is engulfed**
- **Spore coat forms**
- **Mother cell is lysed**
- **Spore is released**

**MOTHER CELL**
- Holoenzyme contains $\sigma^4$ or $\sigma^{43}$

**FORESPORE**
- Phosphorelay activates synthesis of $\sigma^F$ and $\sigma^{pro-E}$
  - $\sigma^E$ is activated and displaces $\sigma^{43}$
  - $\sigma^K$ gene is created; it is transcribed by $\sigma^E$
  - $\sigma^{43}$ is product of early sporulation gene
  - $\sigma^K$ is activated and displaces $\sigma^F$
  - Activated $\sigma^K$ sponsors transcription of late genes

- $\sigma^F$ replaces $\sigma^{43}$ on core enzyme
- $\sigma^F$-core complex transcribes early sporulation genes
- $\sigma^G$ is activated and displaces $\sigma^F$
- Activated $\sigma^G$ sponsors transcription of late genes

Sporulation occurs through an ordered series of sigma production ordered events.
Sporulation Is Controlled by Sigma Factors

Sporulation occurs through an ordered series of events. 

1. Vegetative bacterium
2. DNA replicates
3. Septum forms
4. DNA translocates into forespore
5. Spore is engulfed
6. Spore coat forms
7. Mother cell is lysed
8. Spore is released

**Diagram:**
- **Mother Cell**: Contains σ^K and σ^F.
- **Forespore**: σ^K gene is created; it is transcribed by σ^E.
- Phosphorelay activates synthesis of σ^F and σ^pro-E.
- σ^E is activated and displaces σ^A3.
- σ^K replaces σ^A3 on core enzyme.
- σ^F replaces σ^A3.
- σ^F-core complex transcribes early sporulation genes.
- σ^G is the product of early sporulation gene.
- σ^G is activated and displaces σ^F.
- Activated σ^K sponsors transcription of late genes.

Sporulation occurs through an ordered series of ordered events.
The activities of the different sigma factors are regulated by different mechanisms.

**anti-sigma factor** – A protein that binds to a sigma factor to inhibit its ability to utilize specific promoters.

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*E. coli* has several sigma factors
The mode of control of \( \text{sigma}^{54} \) (the gene product of \( ntrA \) or \( rpoN \)) is achieved, because (unlike \( \text{sigma}^{70} \)) \( \text{sigma}^{54} \) cannot function alone—it requires interaction with another protein NtrC (NRI), which is the gene product of the \( ntrC \) gene.

Moreover, it is not just the NtrC (NRI) that is required, because NRI has to be activated into NR\(_1\)-phosphate by becoming phosphorylated.

NRI is a DNA binding protein which, when phosphorylated, binds to specific sequences of DNA and confers initiation activity on \( \text{sigma}^{54} \), promoting the polymerase's ability to form the Rpol/promoter "open complex". These binding sites do not have to be proximal to the promoter...protein interactions at a distance!!!
Alternative Regulatory Mechanisms Through Alternative Sigma Factors…….

The mode of control of sigma^{54} (the gene product of *ntrA* or *rpoN*) is achieved, because (unlike sigma^{70}) sigma^{54} cannot function alone—it requires interaction with another protein NtrC (NR_{I}), which is the gene product of the *ntrC* gene. Moreover, it is not just the NtrC (NR_{I}) that is required, because NR_{I} has to be activated into NR_{I}-phosphate by becoming phosphorylated.

NR_{I} is a DNA binding protein which, when phosphorylated binds to specific sequences of DNA and confers initiation activity on sigma^{54}, promoting the polymerase's ability to form the Rpol/promoter "open complex". These binding sites do not have to be proximal to the promoter...protein interactions at a distance!!!
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The question now is how does NR$_I$ become phosphorylated?
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Herein, finally lies the connection between specific transcriptional initiation factors and levels of nitrogen in the cell.

$NR_{II}$ is the gene product of $ntrB$ ($glnL$ in $E. coli$), and relates to nitrogen regulation by $ntrC$ in that $NR_{II}$ is a member of the same operon as glutamine synthetase ($glnA$), which is responsible for converting glutamate into glutamine in the presence of $NH_4^+$. 
The mode of control of sigma 54 (the gene product of *ntrA* or *rpoN*) is achieved, because (unlike sigma 70) sigma 54 cannot function alone—it requires interaction with another protein NtrC (NRRI), which is the gene product of the *ntrC* gene. Moreover, it is not just the NtrC (NRRI) that is required, because NRRI has to be activated into NRRI-phosphate by becoming phosphorylated.

NRRI is a DNA binding protein which, when phosphorylated, binds to specific sequences of DNA and confers initiation activity on sigma 54, promoting the polymerase’s ability to form the Rpol/promoter "open complex." These binding sites do not have to be proximal to the promoter...

The question now is how does NRRI become phosphorylated? Through the action of NRRII of course, which is a kinase that responds to levels of NH$_4^+$ in the cell.

Herein, finally lies the connection between specific transcriptional initiation factors and levels of nitrogen in the cell.

NRRII is the gene product of *ntrB* (*glnL* in *E. coli*), and relates to nitrogen regulation by *ntrC* in that NRRII is a member of the same operon as glutamine synthetase (*glnA*), which is responsible for converting glutamate into glutamine in the presence of NH$_4^+$.
The question now is how does $\text{NR}_I$ become phosphorylated? Through the action of $\text{NR}_II$, of course, which is a kinase that responds to levels of $\text{NH}_4^+$ in the cell.

Herein, finally lies the connection between specific transcriptional initiation factors and levels of nitrogen in the cell.

$\text{NR}_II$ is the gene product of $\text{ntrB}$ ($\text{glnL}$ in $\text{E. coli}$), and relates to nitrogen regulation by $\text{ntrC}$ in that $\text{NR}_II$ is a member of the same operon as glutamine synthetase ($\text{glnA}$), which is responsible for converting glutamate into glutamine in the presence of $\text{NH}_4^+$. 

Alternative Regulatory Mechanisms Through Alternative Sigma Factors…….
The mode of control of sigma 54 (the gene product of \textit{ntrA} or \textit{rpoN}) is achieved, because (unlike sigma 70) sigma 54 cannot function alone—it requires interaction with another protein NtrC (NRI), which is the gene product of the \textit{ntrC} gene. Moreover, it is not just the NtrC (\textit{NR}I) that is required, because \textit{NR}I has to be activated into \textit{NR}I-phosphate by becoming phosphorylated. NRI is a DNA binding protein which, when phosphorylated binds to specific sequences of DNA and confers initiation activity on sigma 54, promoting the polymerase’s ability to form the Rpol/promoter “open complex”. These binding sites do not have to be proximal to the promoter...protein interactions at a distance!!!

The question now is how does \textit{NR}I become phosphorylated? Through the action of \textit{NR}II of course, which is a kinase that responds to levels of NH$_4^+$ in the cell

Herein, finally lies the connection between specific transcriptional initiation factors and levels of nitrogen in the cell.

\textit{NR}II is the gene product of \textit{ntrB} (\textit{glnL} in \textit{E. coli}), and relates to nitrogen regulation by \textit{ntrC} in that \textit{NR}II is a member of the same operon as glutamine synthetase (\textit{glnA}), which is responsible for converting \textit{glutamate} into \textit{glutamine} in the presence of NH$_4^+$.
Eukaryotic Transcription.... Similar Themes, But a Little Different

• In eukaryotes chromatin must be opened before RNA polymerase can bind the promoter.

• Multiple DDRPolymerases

• basal transcription factors – Transcription factors required by RNA polymerase II to form the initiation complex at all RNA polymerase II promoters
  
  – These Factors are identified as TFIIX, where X is a letter.
Eukaryotic RNA Polymerases Consist of Many Subunits

- **RNA polymerase I** synthesizes rRNA in the nucleolus (excluding the 5S rRNA). There are 4 major rRNAs in eukaryotic cells designated by their sedimentation size. The 28S, 5S 5.8S RNAs, which are associated with the large ribosomal subunit and the 18S rRNA, which is associated with the small ribosomal subunit.

- **RNA polymerase II** synthesizes mRNA and some of the small nuclear RNAs (snRNAs) microRNAs (miRNAs) involved in the modulation of gene expression through the alteration of mRNA activity involved in RNA splicing.

  - heterogeneous nuclear RNA (hnRNA) – RNA that comprises transcripts of nuclear genes made primarily by RNA polymerase II; it has a wide size distribution and variable stability.

- **RNA polymerase III** synthesizes 5S rRNA, tRNA’s and additional “small RNAs” (includes the small nuclear RNAs (snRNAs) involved in RNA splicing and the microRNAs (miRNAs) involved in the modulation of gene expression through the alteration of mRNA activity.) in the nucleoplasm.

- **Mitochondrial RNA Polymerase** synthesizes transcripts in the mitochondriandria -a lot like bacterial RNA polymerase.
Eukaryotic RNA Polymerases Consist of Many Subunits

- All eukaryotic RNA polymerases have ~12 subunits and are complexes of ~500 kD.
- Some subunits are common to all three RNA polymerases.
- The largest subunit in RNA Pol II has a CTD (carboxy-terminal domain) consisting of multiple repeats of a heptamer.

RNA polymerase II from yeast has >10 subunits
• TBP is a component of the positioning factor that is required for each of the different types of RNA polymerase to bind their respective promoters.

• The factor for RNA polymerase II is TF\textsubscript{II}D, which consists of TBP and \(~14\) TAFs, with a total mass \(~800\) kD.

FIGURE 08: Polymerases bind via commitment factors
RNA Polymerase I Has a “Bipartite Promoter”

- **non-transcribed spacer** – The region between transcription units in a tandem gene cluster.
- The RNA polymerase I promoter consists of a core promoter and an upstream promoter element (UPE)
- The factor **UBF1** wraps DNA around a protein structure to bring the core and UPE into proximity.
RNA polymerase III has two types of promoter sequences.

- Internal promoters have short consensus sequences located within the transcription unit and cause initiation to occur at a fixed distance upstream.

- Upstream promoters contain three short consensus sequences upstream of the startpoint that are bound by transcription factors.

There are three types of pol III promoters.
- **assembly factors** – Proteins that are required for formation of a macromolecular structure but are not themselves part of that structure.

- TF$\text{III}_A$ and TF$\text{III}_C$ bind to the consensus sequences and enable TF$\text{III}_B$ to bind at the startpoint.

- TF$\text{III}_B$ has TBP as one subunit and enables RNA polymerase to bind.

- **pre-initiation complex** – The assembly of transcription factors at the promoter before RNA polymerase binds in eukaryotic transcription.

Type 1 pol III promoters use TF$\text{III}A/C$

Type 2 internal promoters use TF$\text{III}C$
RNA polymerase II requires general transcription factors (called TFII) to initiate transcription.

RNA polymerase II promoters frequently have a short conserved sequence Py_2 CAPy_5 (the initiator Inr) at the startpoint.

The TATA box is a common component of RNA polymerase II promoters and consists of an A-T-rich octamer located ~25 bp upstream of the startpoint.

The downstream promoter element (DPE) is a common component of RNA polymerase II promoters that do not contain a TATA box (TATA-less promoters).

A core promoter for RNA polymerase II includes the Inr and, commonly, either a TATA box or a DPE.
- It may also contain other minor elements.

A minimal pol II promoter has only two elements.
• TBP is a component of the positioning factor that is required for each type of RNA polymerase to bind its promoter.

• The factor for RNA polymerase II is $\text{TF}_{II}D$, which consists of TBP and $\sim 14$ TAFs, with a total mass $\sim 800 \text{ kD}$. 

FIGURE 08: Polymerases bind via commitment factors
http://biotech.gsu.edu/4564/Regulatory_models.html