Gene Regulatory Network Inference

Regulation in Biology

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Gene Expression Regulation

Gene Expression Regulation: Definition

- **Mechanisms** to **increase/decrease** the **creation** of **gene products**.
- **Wide range** of mechanisms.
- Possibly involving **any gene expression step**.

Gene Expression Regulation: Role

For prokaryotes and eukaryotes, it enables:

- **Adaptability** and **versatility**
- Adaptation to new resources
- Response to external signals
- ...

For **multicellular organisms**:

- Cell differentiation
- Morphogenesis
- ...

Example of regulated stages

- **DNA Modification** (DNA $\rightarrow$ *DNA**):
  - Histone modifications (chromatin modification)
  - DNA methylation (epigenetics)
- **Transcriptional** (DNA $\rightarrow$ RNA)
  - **Transcription factors**
- **Post-transcriptional** (mRNA $\rightarrow$ *mRNA**)
  - mRNA transport, splicing, sequestration, degradation
  - Inhibition based on miRNAs
- **Translational** (mRNA $\rightarrow$ Protein)
  - Ribosomal subunits recruitment

Transcription Factors

Transcription Factors (TF): Definition

- **TF**: **Protein controlling** the **transcription rate** (DNA $\rightarrow$ mRNA)
- Turn **on/off gene expression**.
- **Ensure** the **correct gene expression** along cell/organism's life:
  - **Specific cell(s)**
  - **Appropriate timing**
  - **Right amount**

Functional classification

- **Constitutively active**:
  General TF present in all cells at each time

- **Conditionally active**: Require to be activated
  - **Cell specific** (developmental)
  - **Signal dependent** (external signal $\rightarrow$ activation)

Mechanisms governed by TFs: Examples

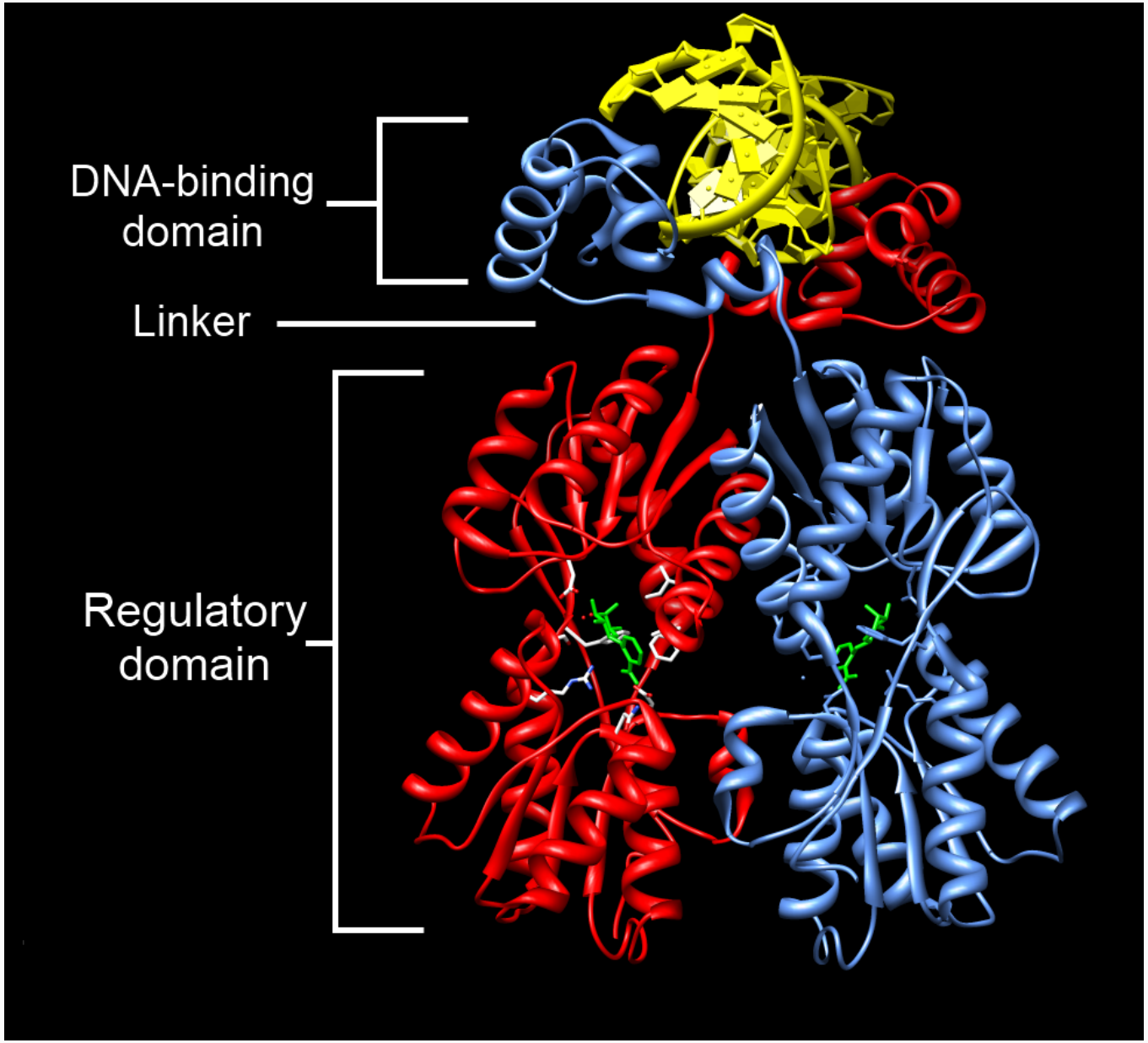
- Cell division
- Cell growth
- Cell death
- Embryogenic development
- Response to external signals (hormones)
- ...

Medical interest

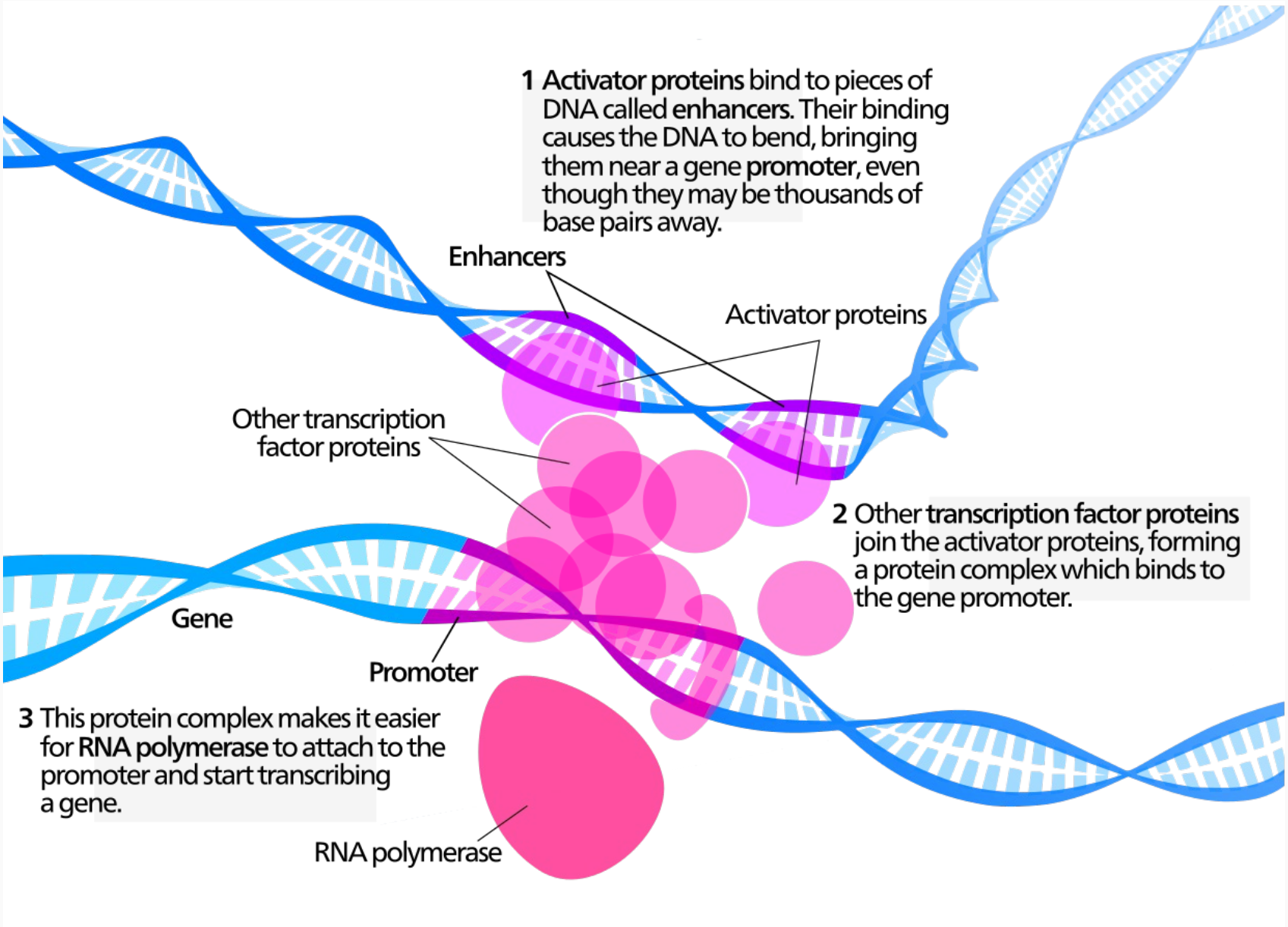
TF mutations $\rightarrow$ specific diseases.

Disease	TFs involved
Cancer	NF-kappaB, AP-1, STAT, HOX
Rett syndrome	MECP2
MODY Diabetes	HNFs, IPF1/Pdx1
Dyspraxia	FOXP2
Autoimmune IPEX disease	FOXP3
...	...

Structure (e.g. LacI dimer)



Mechanism


1 Activator proteins bind to pieces of DNA called enhancers. Their binding causes the DNA to bend, bringing them near a gene promoter, even though they may be thousands of base pairs away.
Enhancers
Activator proteins
Other transcription factor proteins
2 Other transcription factor proteins join the activator proteins, forming a protein complex which binds to the gene promoter.
Gene
Promoter
3 This protein complex makes it easier for RNA polymerase to attach to the promoter and start transcribing a gene.
RNA polymerase

Mechanism

- **Bind** to **specific DNA sequences**
  near its **Target Gene (TG)**
  using a **DNA-binding domain**

- May **Interact** with other **proteins**
  $\rightarrow$ form a **protein complex**
  (e.g., coactivators or corepressors)

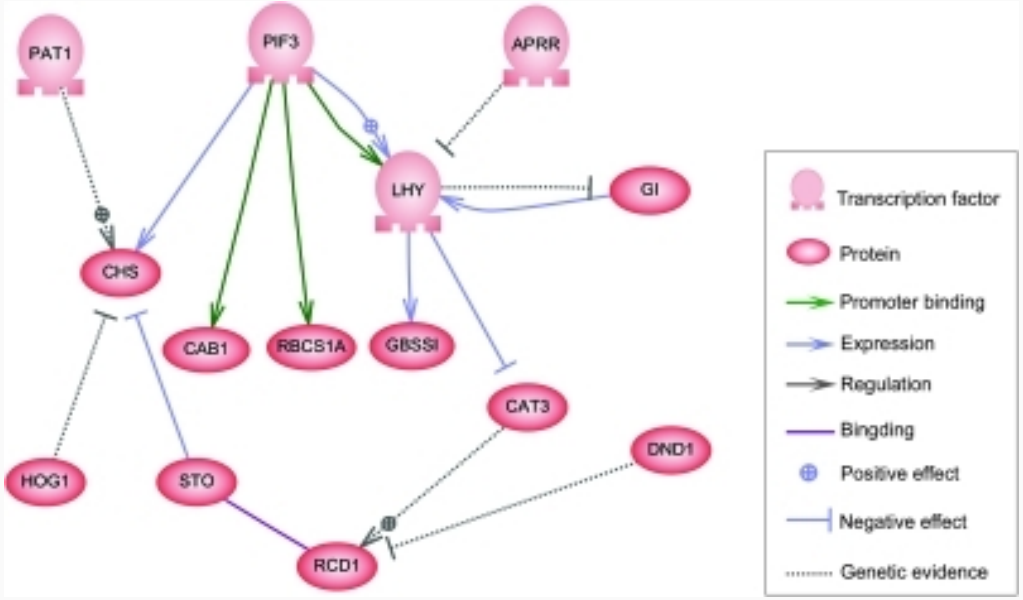
- **Promote** and **stabilize** (activator),
  or **block** (repressor)
  the **recruitment** of **RNA polymerase**.

Gene Regulatory Network

Gene Regulatory Nework: Definition

$G = \langle V, E \rangle$: **oriented graph** with **nodes** V and **edges** E s.t.

- Let V is the set of **genes**.
- Let $R \subset V$ be a set of **regulators**
- $\exists e = (r, v) \in E$ if :
  $r \in R$ controls the **gene expression** of v.



Topology

- **Few hubs** (highly connected nodes)
- **Several scarcely** connected **nodes**
- **Sparse connectivity**
- **Network topology**: **Hierarchical Scale free**
- Presence of **network motifs**
  (e.g., feed-forward motifs).

Evolution of GRNs

- **Addition** or **subtraction** of **genes**.
- **Preferential attachment** of **duplicated genes** to **hub genes**.
- Entire **modules** (sub-graphs) are expressed in **different contexts**.