



Escuela Superior de Administración y Comercio Unidad Tepepan

***“Dinámica No-Lineal: Aplicaciones en
fisiología”***

I.Q. Jesús Andrés Arzola Flores



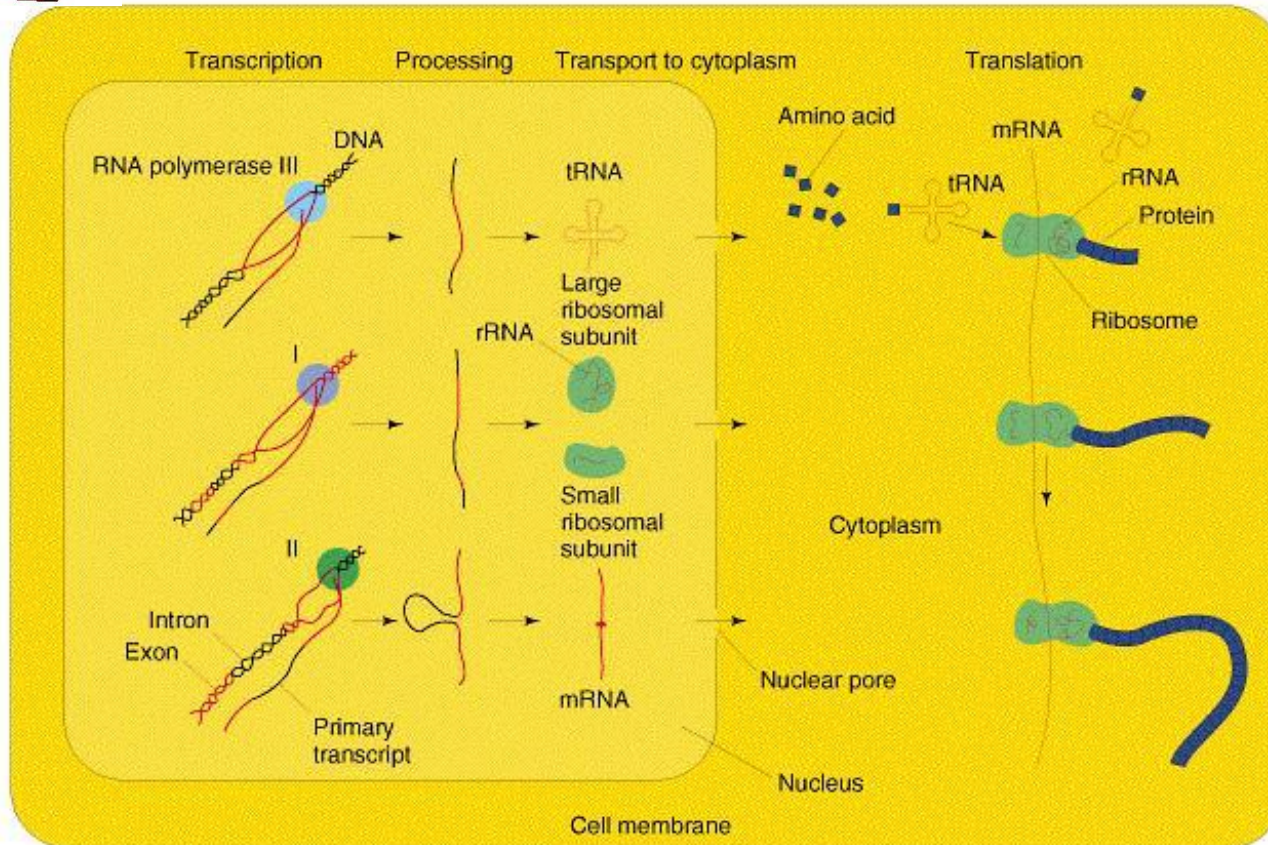
Resumen

- La interacción entre mRNA, sRNA, y las proteínas desempeña un papel crucial en la regulación de genes.
- En esta investigación se exploró la dinámica de dos arquitecturas mínimas mediadas por sRNAs.
- Se introdujeron y se compararon dos escenarios en los cuales el sRNA opera diferente, es decir, la represión post-transcripcional y la represión de traducción.
- Se planteó un tercer escenario que ejemplifica la coexistencia de los dos anteriores escenarios y se obtuvo el modelo matemático del tercer escenario.
- Se resolvieron numéricamente los tres escenarios y se encontró que en los tres casos, existen dinámicas complejas.

Dengyu Liu, Xiao Chang¹, Zengrong Liu, Luonan Chen, Ruiqi Wang., “Bistability and Oscillations in Gene Regulation Mediated by Small Noncoding RNAs” PLoS ONE. (2011).

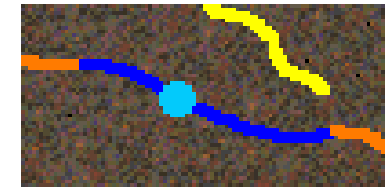


Formación de RNA



(b) Eukaryote

En la figura animada de la derecha el molde de DNA aparece de color azul, la RNA-polimerasa de color celeste, y el transcrito primario de RNA de color amarillo



Transcrito primario



sRNA

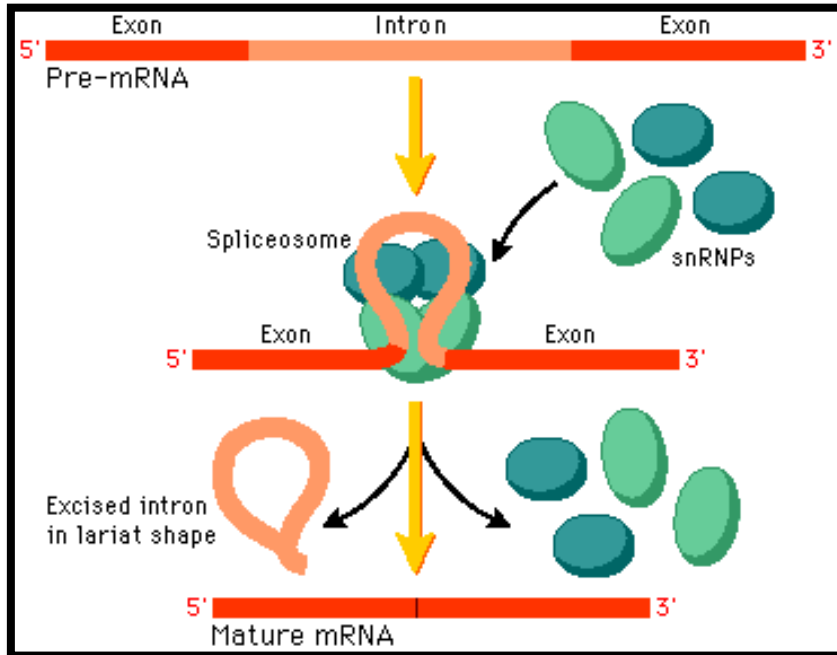


Figura 2. Formación de Spliceosome

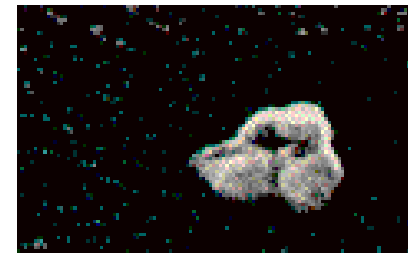
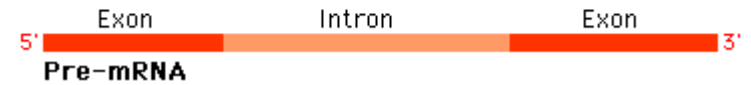
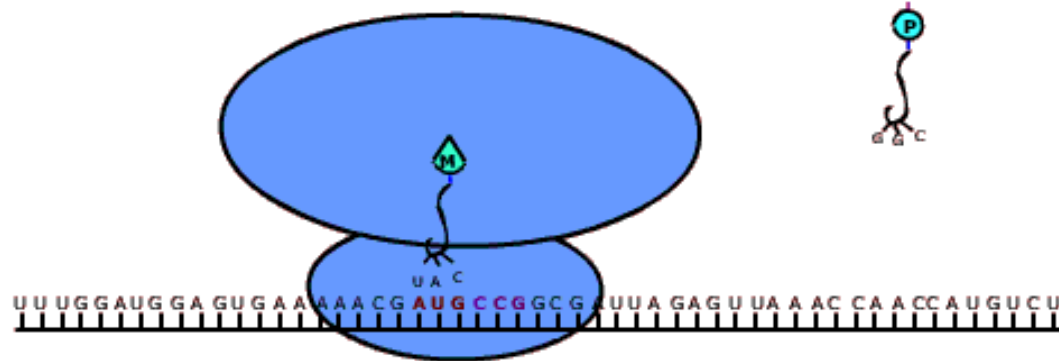


Figura 3. Spliceosome (microscopio electrónico).

B. Alberts., “Biología molecular de la célula”, Tercera edición., Editoriales OMEGA.



mRNA



- Se sintetiza sobre un molde de DNA y sirve de pauta para la síntesis de proteínas (**traducción**).
- Su peso molecular es alto y contiene únicamente los nucleótidos A, U, G y C. Además de contener codificada la secuencia de una proteína, contiene señales para la **iniciación** y **terminación** de la síntesis.
- Presenta en su **extremo 5'** una estructura compleja llamada "**capucha**" (cap), y en su **extremo 3'** una cadena de **poliA** de longitud variable. Estas modificaciones tienen por objeto aumentar la vida media de estas moléculas en el citoplasma.

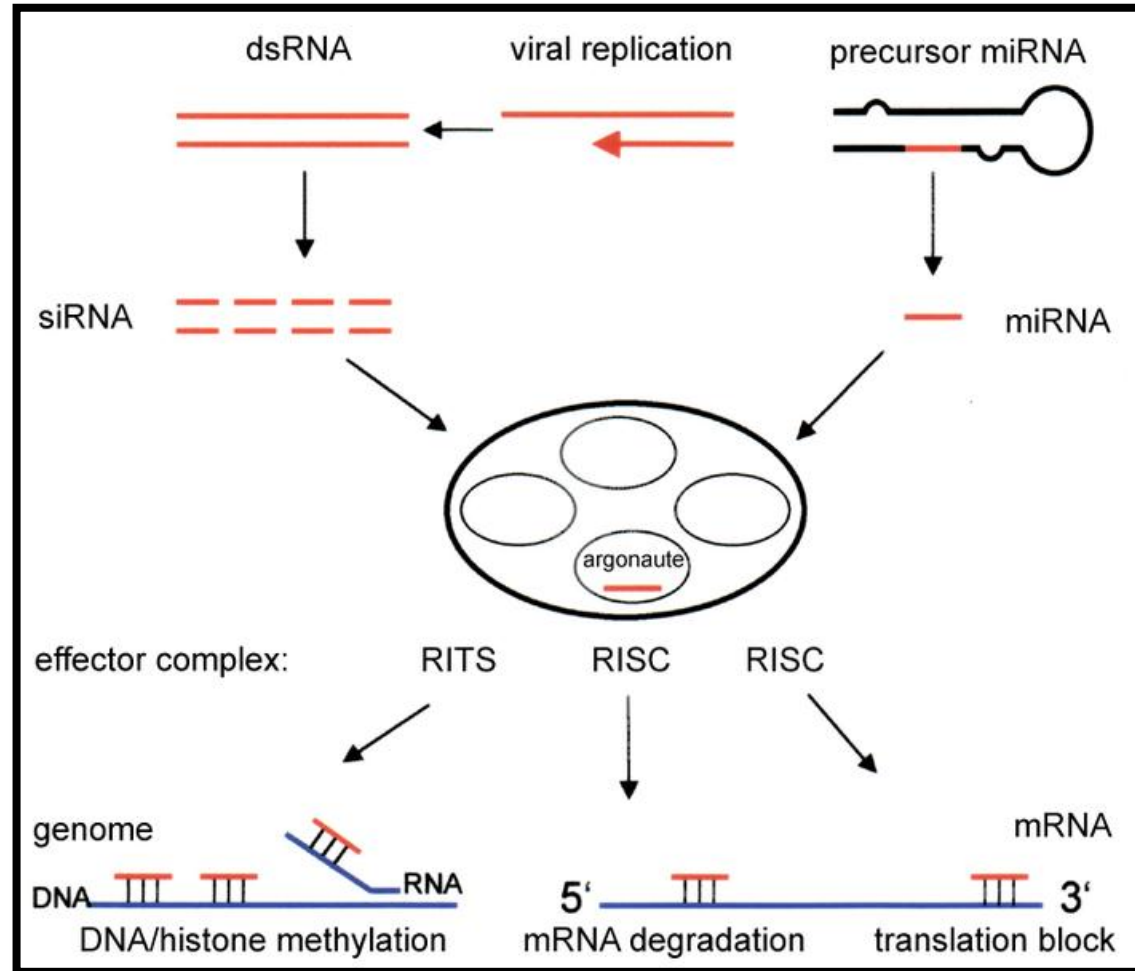
B. Alberts., "Biología molecular de la célula"., Tercera edición., Editoriales OMEGA.



siRNA



- **RNA pequeño de interferencia** o **RNA de silenciamiento**.
- Es altamente específico para la secuencia de nucleótidos de su mRNA diana, interfiriendo por ello con la expresión del gen respectivo.

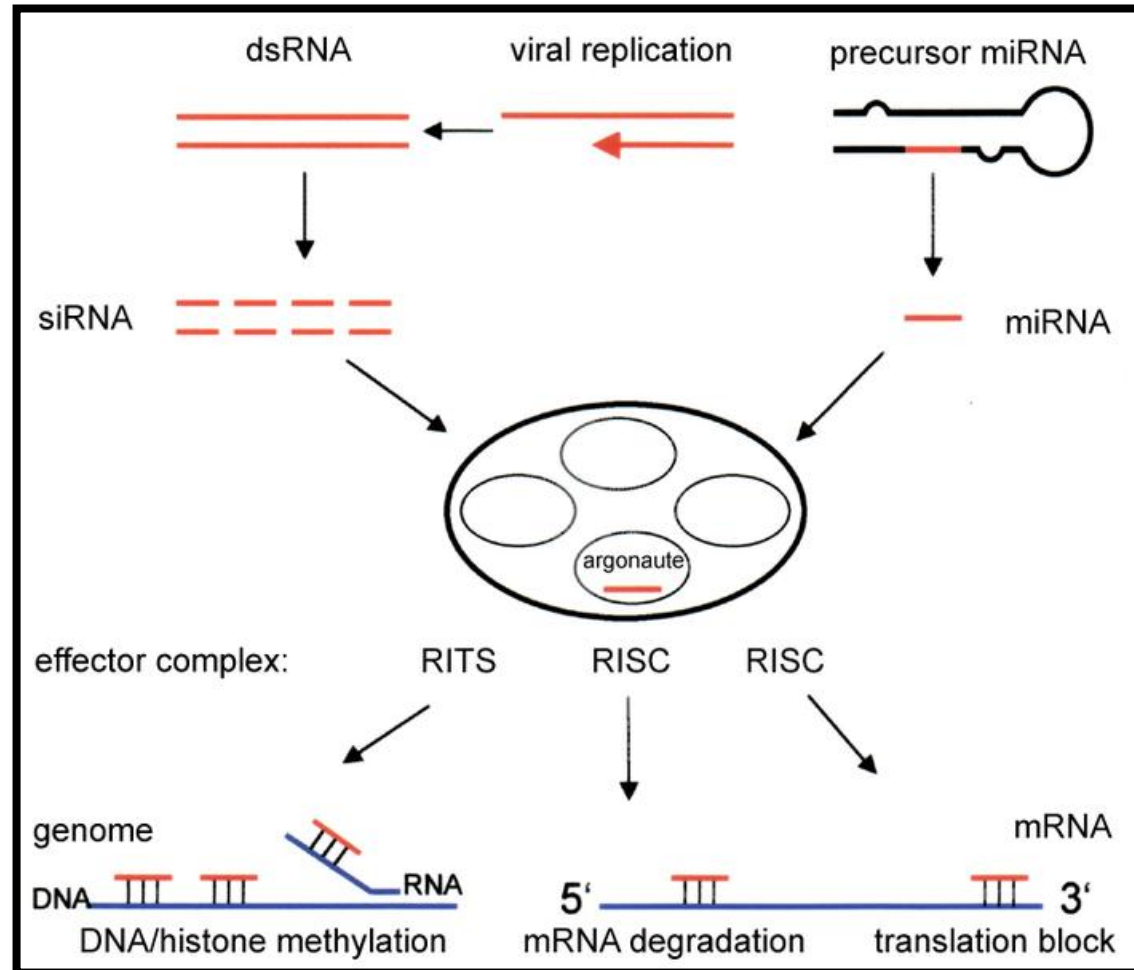




siRNA



- Suprimen la expresión de los genes diana mediante el corte del RNA mensajero (mRNA) complementario en dos mitades, a través de la interacción de la hebra antisentido del siRNA con el complejo RISC (*RNA-induced silencing complex*).





Mecanismo de defensa



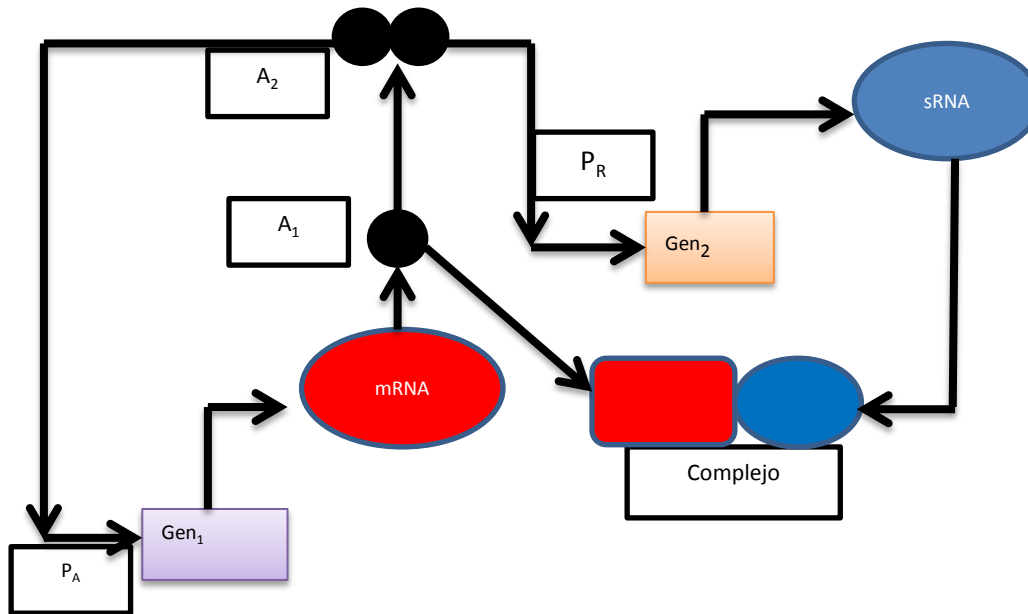
Figura 5. Un mecanismo de defensa en las plantas, de forma que éstas responden a la infección de los retrovirus mediante la destrucción de los ARN virales.



1er Comportamiento de estudio



P-siRNA



Donde:

P_R: Precursor de sRNA.

P_A: Precursor de mRNA.

A₁ y A₂: Proteínas.

P_RA₁: Precursor de sRNA activado.

P_AA₂: Precursor de mRNA activado.

m_A: mRNA.

m_R: sRNA.

Φ: Complejo inactivo.

Figura 4. a) Escenario I, el complejo que inactiva la reacción se forma por la interacción P-sRNA.

Traducción.

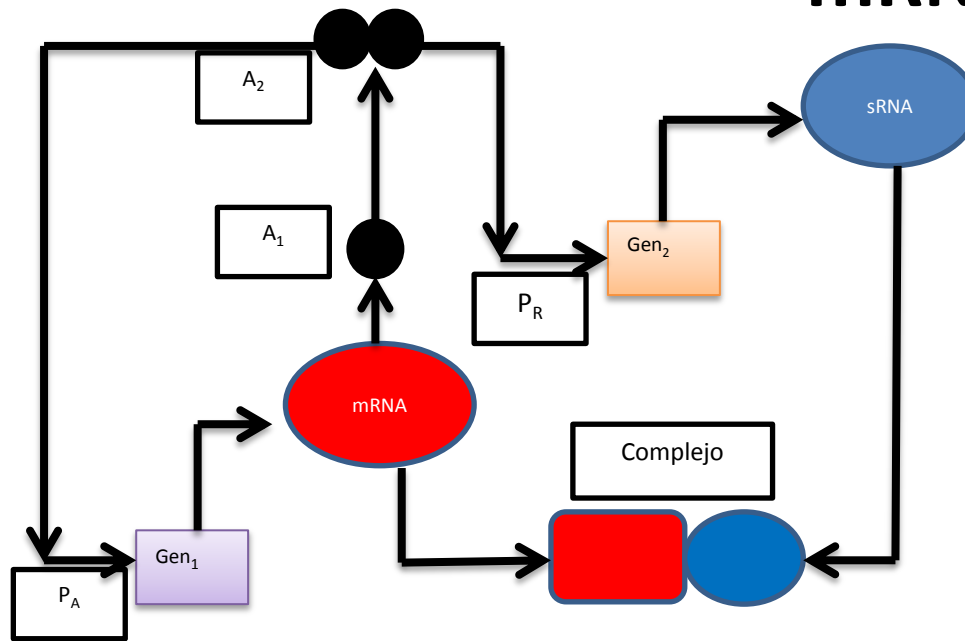
Dengyu Liu, Xiao Chang¹, Zengrong Liu, Luonan Chen, Ruiqi Wang., "Bistability and Oscillations in Gene Regulation Mediated by Small Noncoding RNAs" PLoS ONE. (2011).



2do Comportamiento de estudio



mRNA-RISC-siRNA



Donde:

P_R : Precursor de sRNA.

P_A : Precursor de mRNA.

A_1 y A_2 : Proteínas.

P_{RA_1} : Precursor de sRNA activado.

P_{AA_2} : Precursor de mRNA activado.

m_A : mRNA.

m_R : sRNA.

Φ : Complejo inactivo.

Figura 5. b) Escenario II, el complejo que inactiva la reacción se forma por la interacción RNAm-sRNA.

Post-Transcripción.

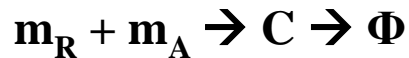
Dengyu Liu, Xiao Chang¹, Zengrong Liu, Luonan Chen, Ruiqi Wang., "Bistability and Oscillations in Gene Regulation Mediated by Small Noncoding RNAs" PLoS ONE. (2011).



Modelos

- 1) $DNA_1 \rightarrow DNA_1 + mRNA$
- 2) $DNA_2 \rightarrow DNA_2 + sRNA$
- 3) $mRNA \rightarrow mRNA + P$
- 4) $P + P \rightarrow P_2$
- 5) $P_2 \rightarrow P + P$
- 6) $mRNA + sRNA \rightarrow mRNA$
- 7) $mRNA \rightarrow \Phi$
- 8) $P \rightarrow \Phi$

Escenario I



Escenario II



Dengyu Liu, Xiao Chang¹, Zengrong Liu, Luonan Chen, Ruiqi Wang., "Bistability and Oscillations in Gene Regulation Mediated by Small Noncoding RNAs" PLoS ONE. (2011).

**Comportamiento I:
P-siRNA**

$$\frac{dx}{dt} = \gamma y - \delta x,$$

$$\frac{dy}{dt} = \lambda \frac{1 + \rho x^2}{1 + x^2} - \alpha y - \sigma yz,$$

$$\frac{dz}{dt} = \mu \frac{1 + \rho x^2}{1 + x^2} - \beta z - \sigma yz,$$

Comportamiento II: mRNA-RISC-siRNA

$$\frac{dx}{dt} = \gamma y - \delta x - \sigma xz,$$

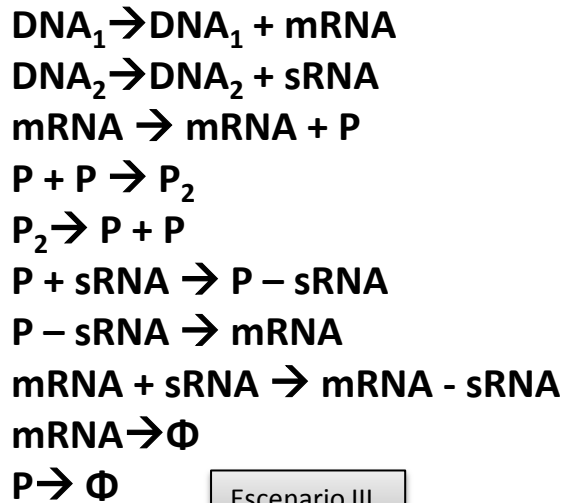
$$\frac{dy}{dt} = \lambda \frac{1 + \rho x^2}{1 + x^2} - \alpha y,$$

$$\frac{dz}{dt} = \mu \frac{1 + \rho x^2}{1 + x^2} - \beta z - \sigma xz$$

$x=[Proteína], y=[mRNA], z=[sRNA]$



Generalización ¿Coexistencia?



Escenario III

$$\frac{dx}{dt} = \gamma y - \delta x - \sigma xz$$

$$\frac{dy}{dt} = \lambda \left[\frac{1 + \rho x^2}{1 + x} \right] - \alpha y + \sigma xz$$

$$\frac{dz}{dt} = \mu \left[\frac{1 + \rho x^2}{1 + x} \right] - \beta z - \sigma xz$$

$x=[\text{Proteína}], y=[\text{mRNA}], z=[\text{sRNA}]$

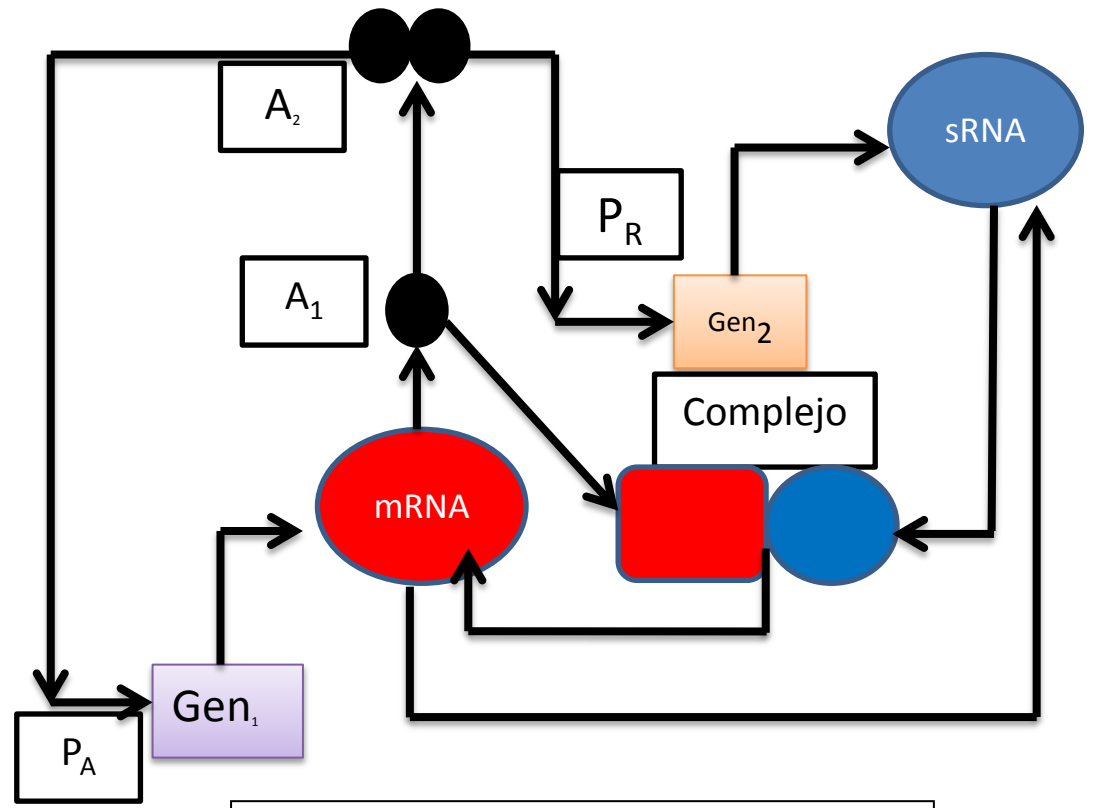


Figura 6. Los dos mecanismos coexisten

Dengyu Liu, Xiao Chang¹, Zengrong Liu, Luonan Chen, Ruiqi Wang., "Bistability and Oscillations in Gene Regulation Mediated by Small Noncoding RNAs" PLoS ONE. (2011).



Reducción

$$\frac{dy}{dt} = \lambda \left[\frac{1 + \rho \left(\frac{\gamma y}{(\delta + \sigma z)} \right)^2}{1 + \left(\frac{\gamma y}{(\delta + \sigma z)} \right)} \right] - \alpha y$$

$y=[\text{mRNA}], z=[\text{sRNA}]$

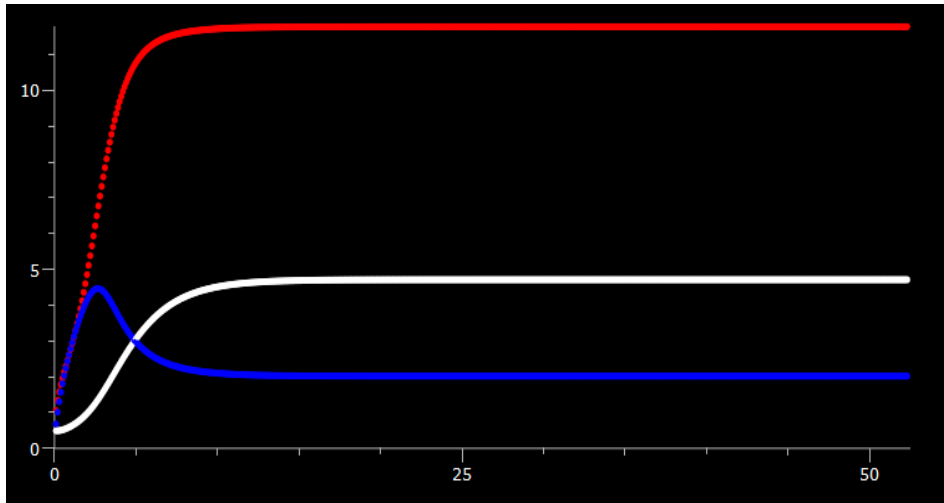
$$\frac{dz}{dt} = \mu \left[\frac{1 + \rho \left(\frac{\gamma y}{(\delta + \sigma z)} \right)^2}{1 + \left(\frac{\gamma y}{(\delta + \sigma z)} \right)} \right] - \beta z - \sigma \left[\frac{\gamma y}{(\delta + \sigma z)} \right] z$$

Dengyu Liu, Xiao Chang¹, Zengrong Liu, Luonan Chen, Ruiqi Wang., "Bistability and Oscillations in Gene Regulation Mediated by Small Noncoding RNAs" PLoS ONE. (2011).



Resultados

$$\frac{dx}{dt} = \gamma y - \delta x,$$



$$\frac{dy}{dt} = \lambda \frac{1 + \rho x^2}{1 + x^2} - \alpha y - \sigma yz,$$

$$\frac{dz}{dt} = \mu \frac{1 + \rho x^2}{1 + x^2} - \beta z - \sigma yz,$$

Figura 7. Solución numérica del escenario I. Se observa estabilización de las concentraciones proteína (línea blanca), mRNA (línea azul) y sRNA (línea roja). Concentraciones iniciales $x=0.5$, $y= 0.7$ y $z= 0.3$. Los valores de los parámetros fueron los siguientes: $\lambda=0.6$, $\delta= 0.5$, $\gamma=0.2$, $\alpha=2$, $\mu= 0.5$, $\beta= 0.3$, $\rho= 40$ y $\sigma= 2$.

Método numérico empleado para resolver las ecuaciones del escenario I es Runge-Kutta con un paso de tiempo $dt=0.1$ con parámetros. Los valores de los parámetros fueron los siguientes: $\lambda=0.6$, $\delta= 0.5$, $\gamma=0.2$, $\alpha=2$, $\mu= 0.5$, $\beta= 0.3$, $\rho= 40$ y $\sigma= 2$. y se realizaron 2400 iteraciones para obtener la solución de los modelos matemáticos de los tres escenarios.



Resultados



$$\frac{dx}{dt} = \gamma y - \delta x - \sigma xz,$$

$$\frac{dy}{dt} = \lambda \frac{1 + \rho x^2}{1 + x^2} - \alpha y,$$

$$\frac{dz}{dt} = \mu \frac{1 + \rho x^2}{1 + x^2} - \beta z - \sigma xz$$

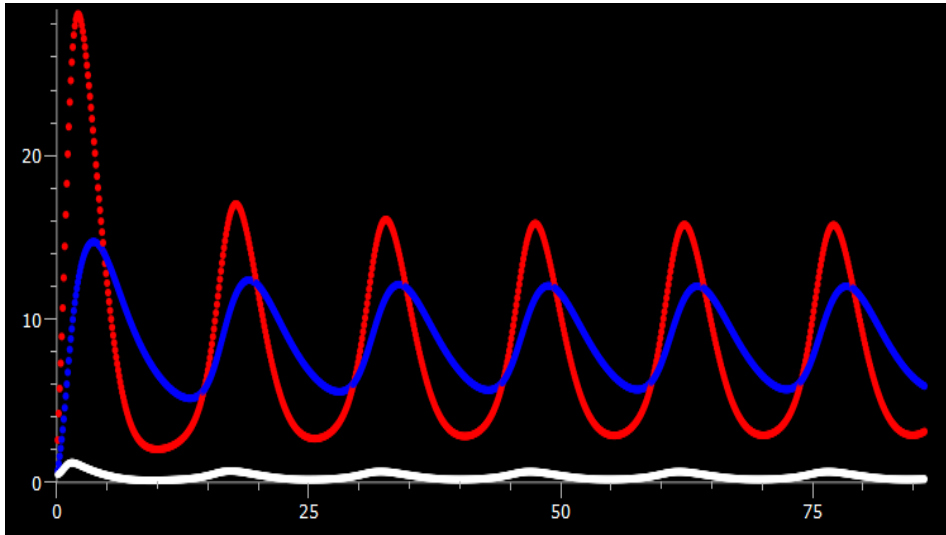
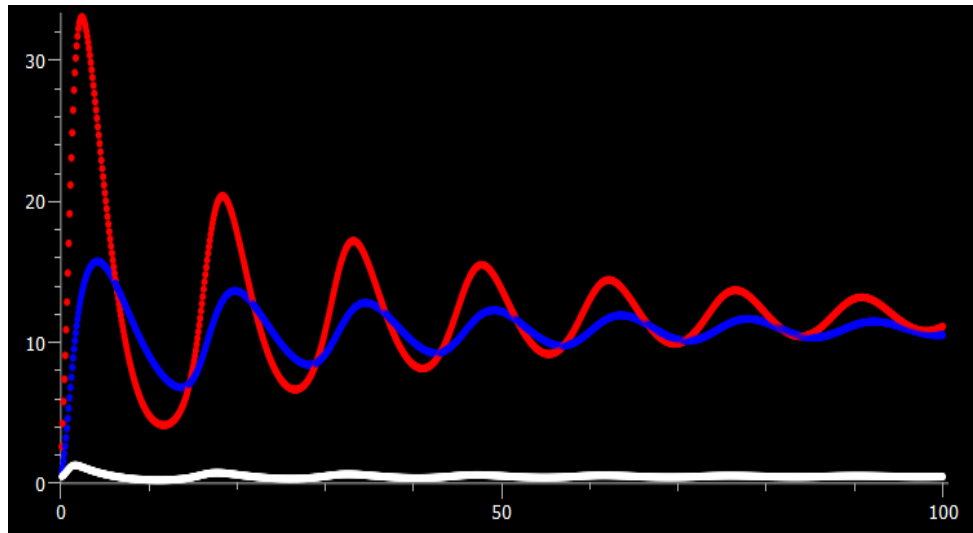


Figura 8. Solución numérica del escenario II. Se observan oscilaciones de las concentraciones proteína (línea blanca), mRNA (línea azul) y sRNA (línea roja). Concentraciones iniciales $x=0.5$, $y= 0.7$ y $z= 0.3$. Los valores de los parámetros fueron los siguientes: $\lambda=2.5$, $\delta= 0.5$, $\gamma=0.2$, $\alpha=2$, $\mu= 0.5$, $\beta= 0.3$, $\rho= 40$ y $\sigma= 0.4$.

Método numérico empleado para resolver las ecuaciones del escenario II es Runge-Kutta con un paso de tiempo $dt=0.1$ con parámetros. Los valores de los parámetros fueron los siguientes: $\lambda=2.5$, $\delta= 0.5$, $\gamma=0.2$, $\alpha=2$, $\mu= 0.5$, $\beta= 0.3$, $\rho= 40$ y $\sigma= 0.4$.



Resultados



$$\frac{dx}{dt} = \gamma y - \delta x - \sigma xz$$

$$\frac{dy}{dt} = \lambda \left[\frac{1 + \rho x^2}{1 + x} \right] - \alpha y + \sigma xz$$

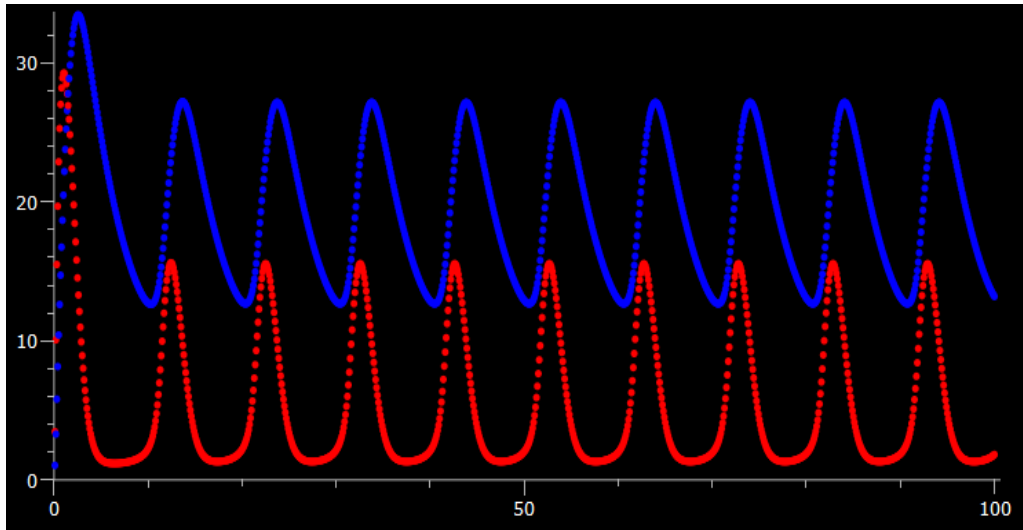
$$\frac{dz}{dt} = \mu \left[\frac{1 + \rho x^2}{1 + x} \right] - \beta z - \sigma xz$$

Figura 9. Solución numérica del escenario III. Se observan oscilaciones de las concentraciones proteína (línea blanca), mRNA (línea azul) y sRNA (línea roja), seguidas de un estado de estabilización. Concentraciones iniciales $x=0.5$, $y= 0.7$ y $z= 0.3$. Los valores de los parámetros fueron los siguientes: $\lambda=2.5$, $\delta= 0.5$, $\gamma=0.2$, $\alpha=2$, $\mu= 0.5$, $\beta= 0.3$, $\rho= 40$ y $\sigma= 0.4$.

Método numérico empleado para resolver las ecuaciones del escenario III es Runge-Kutta con un paso de tiempo $dt=0.1$ con parámetros. Los valores de los parámetros fueron los siguientes: $\lambda=2.5$, $\delta= 0.5$, $\gamma=0.2$, $\alpha=2$, $\mu= 0.5$, $\beta= 0.3$, $\rho= 40$ y $\sigma= 0.4$.



Resultados



$$\frac{dy}{dt} = \lambda \left[\frac{1 + \rho \left(\frac{\gamma y}{(\delta + \sigma z)} \right)^2}{1 + \left(\frac{\gamma y}{(\delta + \sigma z)} \right)} \right] - \alpha y$$

$$\frac{dz}{dt} = \mu \left[\frac{1 + \rho \left(\frac{\gamma y}{(\delta + \sigma z)} \right)^2}{1 + \left(\frac{\gamma y}{(\delta + \sigma z)} \right)} \right] - \beta z - \sigma \left[\frac{\gamma y}{(\delta + \sigma z)} \right] z$$

Figura 10. Solución numérica del escenario II (Modelo matemático reducido). Se observan oscilaciones de las concentraciones de mRNA (línea azul) y sRNA (línea roja). Concentraciones iniciales $y= 0.7$ y $z= 0.3$. Los valores de los parámetros fueron los siguientes: $\lambda=2$, $\delta= 0.5$, $\gamma=0.2$, $\alpha=2$, $\mu= 0.5$, $\beta= 0.3$, $\rho= 40$ y $\sigma= 0.2$.

Método numérico empleado para resolver las ecuaciones del escenario II reducido es Runge-Kutta con un paso de tiempo $dt=0.1$ con parámetros. Los valores de los parámetros fueron los siguientes: $\lambda=2$, $\delta= 0.5$, $\gamma=0.2$, $\alpha=2$, $\mu= 0.5$, $\beta= 0.3$, $\rho= 40$ y $\sigma= 0.2$.



Conclusiones

- El escenario II demuestra poseer una mejor eficiencia y robustez en la represión de la traducción., debido a que muestra un proceso oscilatorio que ejemplifica perfectamente la dinámica intracelular.
- Este estudio nos ayudará a analizar las complejas redes de interacciones entre macromoléculas intracelulares, montándolas como módulos simples para estudiarlas con mayor facilidad. Este estudio da la pauta para el inicio de un conocimiento más profundo del funcionamiento de sRNA's, que será de interés en la bio-ingeniería y el control artificial.
- El estudio de la dinámica del RNA nos llevará a plantear sistemas de genes homeóticos, los cuales nos ayudarán a construir modelos matemáticos que nos explicarán la compleja forma en la que una célula madre se diferencia.



Perspectivas

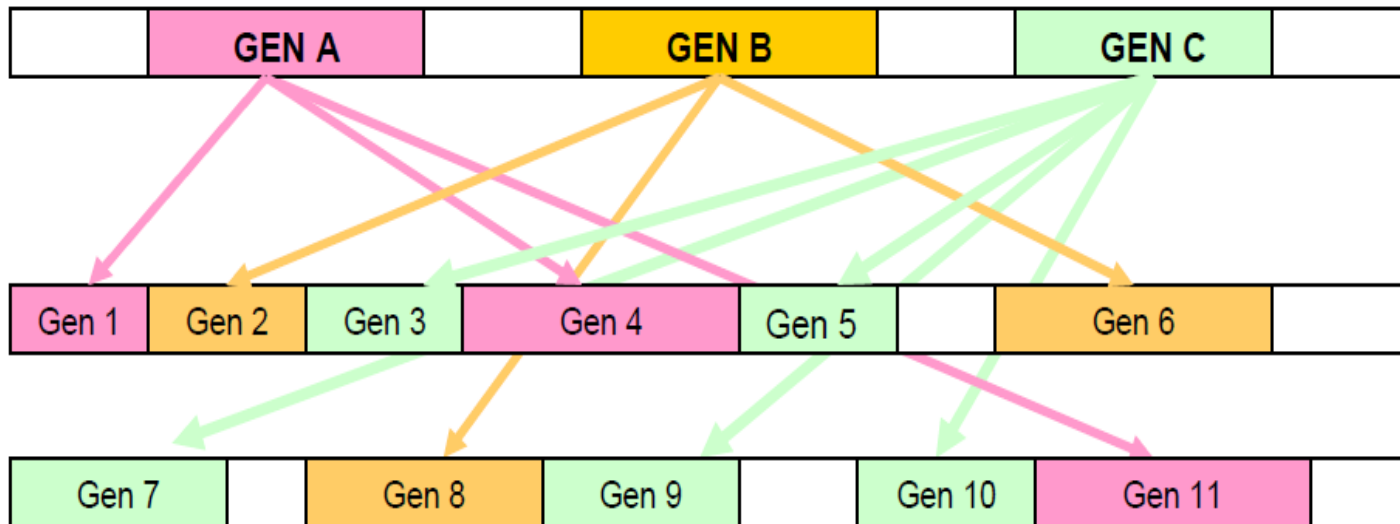


Figura 8. A, B y C son genes homeóticos cuyos productos (proteínas homeóticas) regulan la actividad de sus genes subordinados. Cuando el Gen A está activo, los genes 1, 4 y 11 están “prendidos” los cuales le indican a la célula madre a qué tipo de célula debe convertirse.

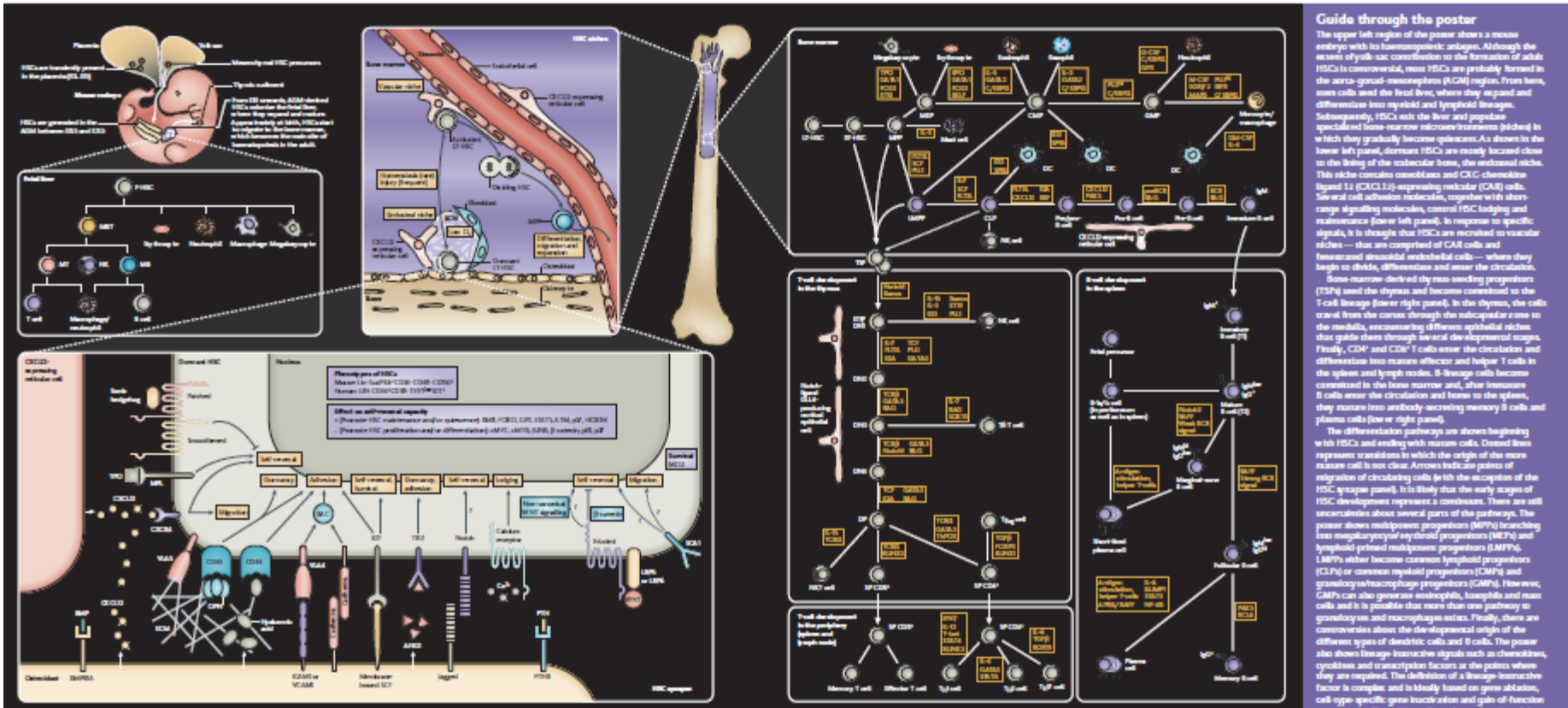


Haematopoietic stem cells, niches and differentiation pathways

Thomas Graf and Andreas Trumpp

Haematopoietic stem cells (HSCs) continuously replenish blood cells that are lost by attrition or tissue damage. They are capable of self-renewal and are currently the only adult stem-cell type routinely used in clinical settings to replace lost cells. HSCs are mostly quiescent but can be mobilized from their niche to proliferate and differentiate into lineages of the innate and adaptive immune system, as well as into red blood cells and platelets. Cell-fate decisions are initiated and maintained by specific combinations of

transcription factors, the activity of which is orchestrated by extrinsic and intrinsic signals. The study of changes in regulatory networks during haematopoietic differentiation has long served as a paradigm for basic processes of cell-fate specification and its aberrations, such as those that occur in leukaemia. The easy access and transplantability of normal and leukaemic haematopoietic cells has led to the discovery of cytokines, oncogenes and cancer stem cells and to some of the most celebrated successes of targeted drug design.



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 - Stem Cells, Mesoderm and Endoderm lineages
 - Wnt, TGF- β , Hedgehog and Notch signalling pathways

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A brief history
 A brief history of stem cell research. Stem cell research has a long and rich history, with the discovery of the first stem cells in the 1960s. The field has since expanded to include a wide range of stem cell types and their applications in regenerative medicine and disease modeling.

Stem cell niches
 Stem cell niches are specialized microenvironments that support the self-renewal and differentiation of stem cells. These niches are found in various tissues and are essential for maintaining the stem cell population.

Stem cell differentiation
 Stem cell differentiation is the process by which stem cells give rise to specialized cell types. This process is regulated by a complex network of transcription factors and signaling pathways.

Guide through the poster

The upper left region of the poster shows a mouse embryo with its haematopoietic progenitors. Although the recent erythroid progenitors contribute to the formation of adult HSCs in conventional, most HSCs are probably formed in the aorta-gonad-mesonephros (AGM) region. From here, stem cells seed the fetal liver, where they expand and differentiate into myeloid and lymphoid lineages. Subsequently, HSCs exit the liver and populate specialized bone marrow microenvironments (niches) in which they gradually become quiescent. As shown in the lower left panel, dormant HSCs are probably located close to the lining of the endosteal bone, the endosteal niche. This niche contains osteoblasts and CXCL12-expressing stromal cells (CXCL12-expressing stromal cells [CSEs]). Several cell adhesion molecules, together with short-range signaling molecules, control HSC lodging and maintenance (see left panel). In response to specific signals, it is thought that HSCs are recruited to vascular niches — that are comprised of CAE cells and fenestrated endothelial cells — where they begin to divide, differentiate and enter the circulation.

Some marrow-derived stem-seeding progenitors (SSPs) seed the thymus and become committed to the T-cell lineage (see right panel). In the thymus, the cells travel from the cortex through the subcapsular zone to the medulla, entering one of two different epithelial niches that guide them through several developmental stages. Finally, CD4⁺ and CD8⁺ T cells enter the circulation and differentiate into mature effector and helper T cells in the spleen and lymph nodes. B lineage cells become committed in the bone marrow and, after immature B cells enter the antibody-secreting memory B cells and plasma cells (see right panel).

The differentiation pathways are shown beginning with HSCs and ending with mature cells. Dotted lines represent transitions in which the origin of the mature stem cell is not clear. Arrows indicate paths of migration of circulating cells to niches in the marrow of the HSC niche panel. It is likely that the early stages of HSC development represent a continuum. There are cell secretions above several parts of the pathways. The poster shows multipotent progenitors (MPPs) branching into megakaryocyte/erythroid progenitors (MEPs) and lymphoid primed multipotent progenitors (LMPPs). LMPPs also become common lymphoid progenitors (CLPs) or common myeloid progenitors (CMPs) and granulocyte/macrophage progenitors (GMPs). However, CMPs can also generate megakaryocytes, megakaryocytes and mast cells and it is possible that more than one pathway to granulocytes and macrophages exist. Finally, there are connections above the developmental origin of the different types of dendritic cells and B cells. The poster also shows lineage-instructive signals such as chemokines, cytokines and transcription factors at the points where they are required. The definition of a lineage-instructive factor is complex and is likely based on gene ablation, cell-type-specific gene knock-out and gain-of-function experiments. Since this applies only to a fraction of the factors shown here, the information provided is somewhat qualitative. Also, only transcription factors that act dominantly during lineage commitment are listed, but not those that have a secondary effect.

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