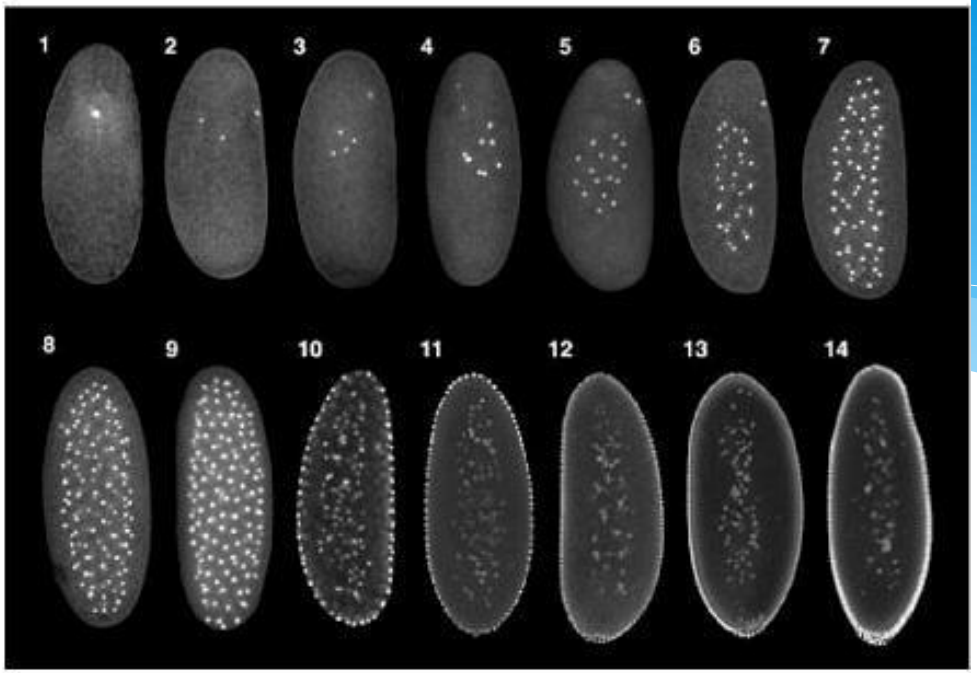
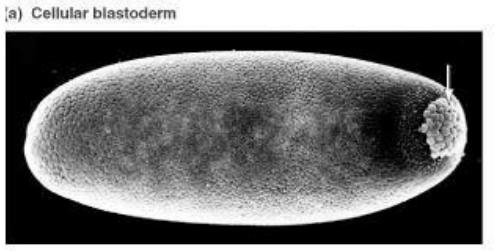
La specificazione del sistema nervoso negli insetti

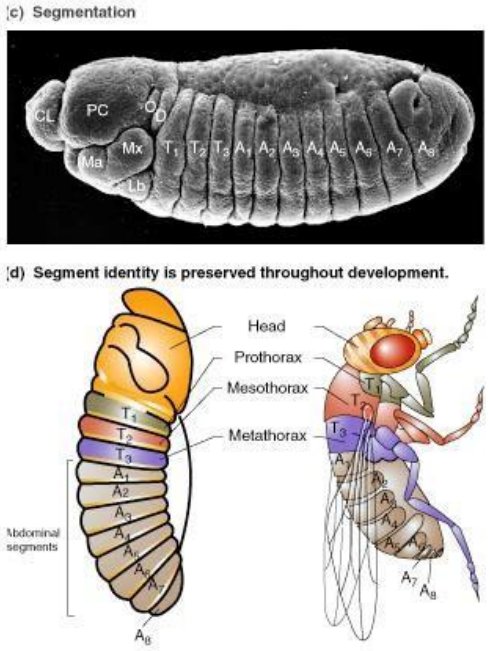


Segmentazione

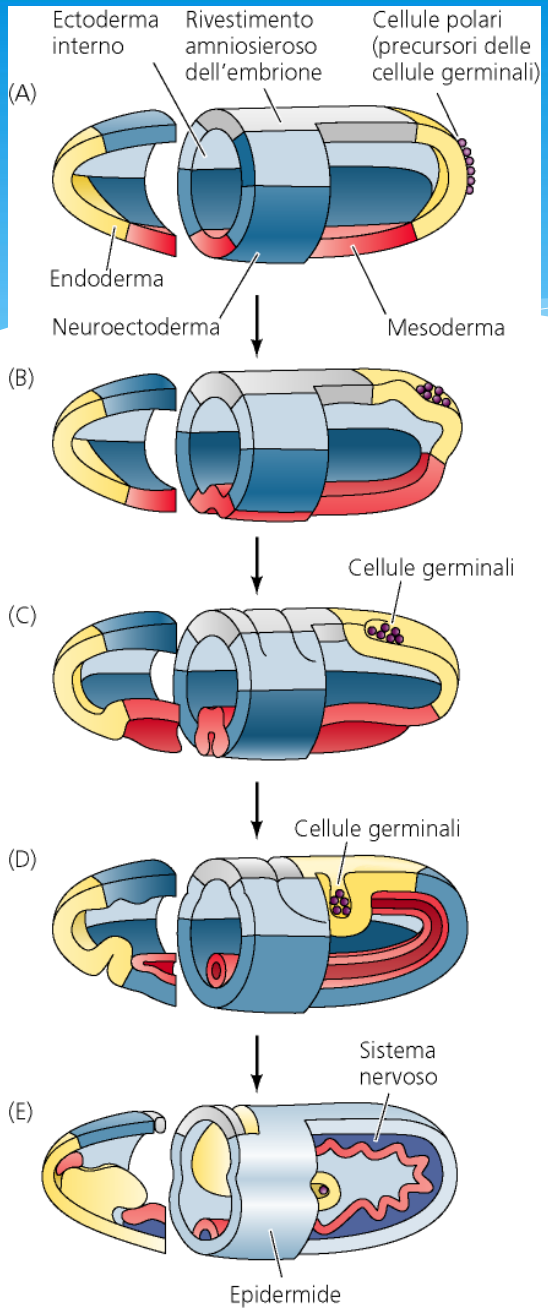


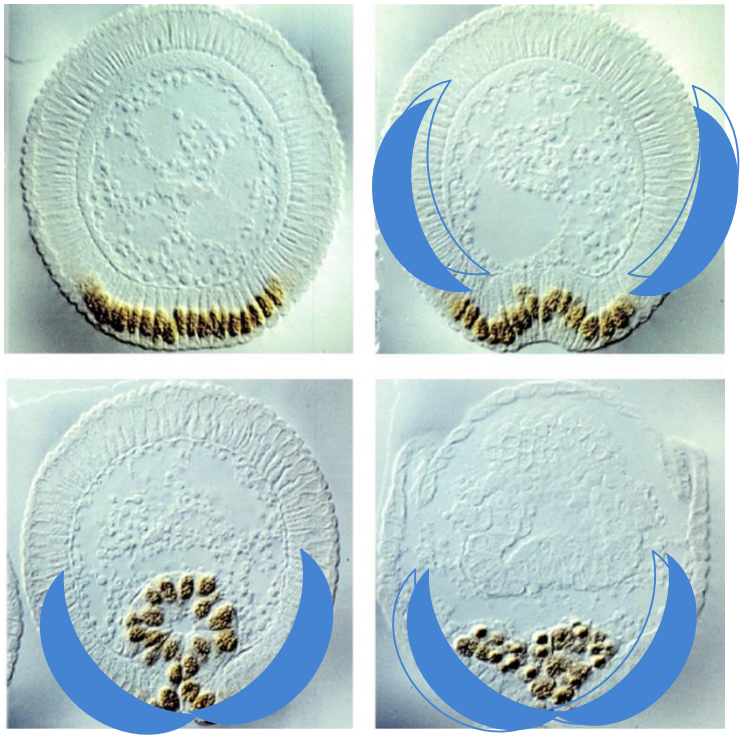
gastrulazione



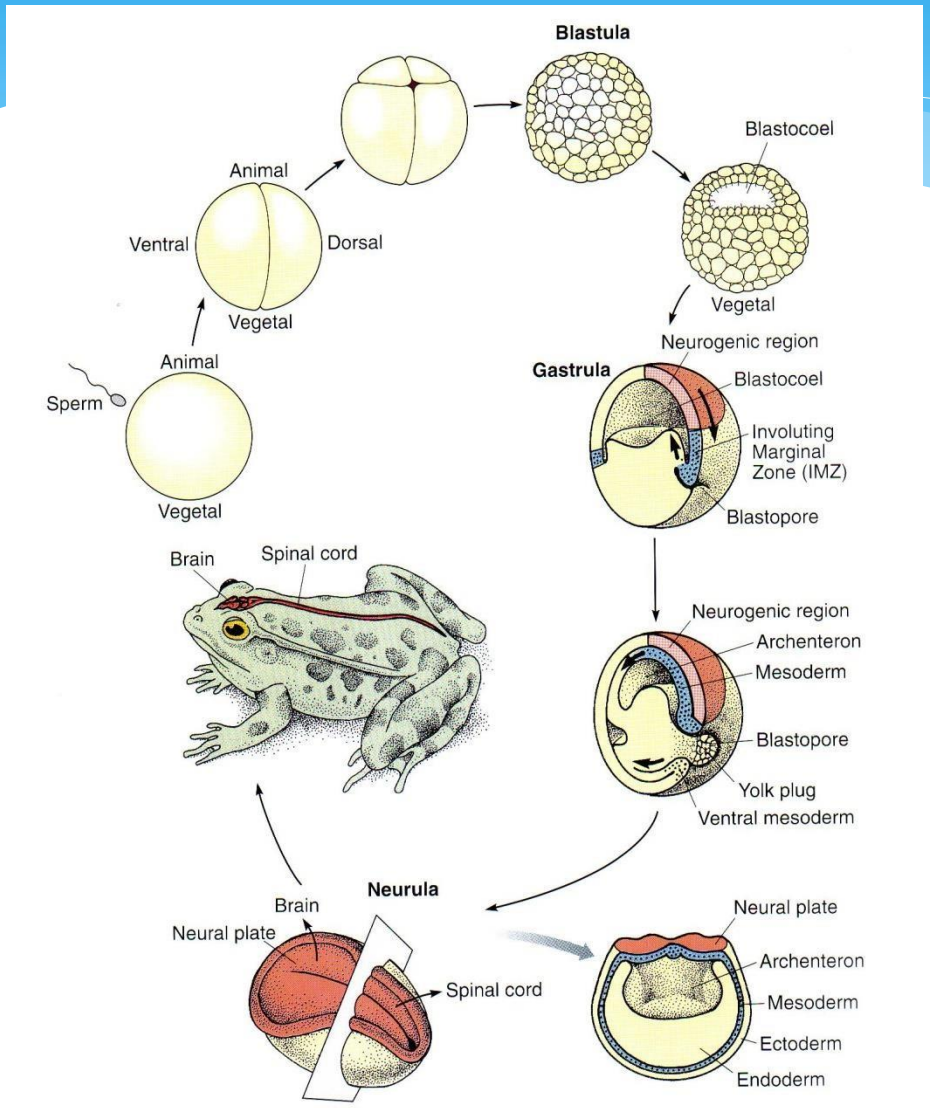


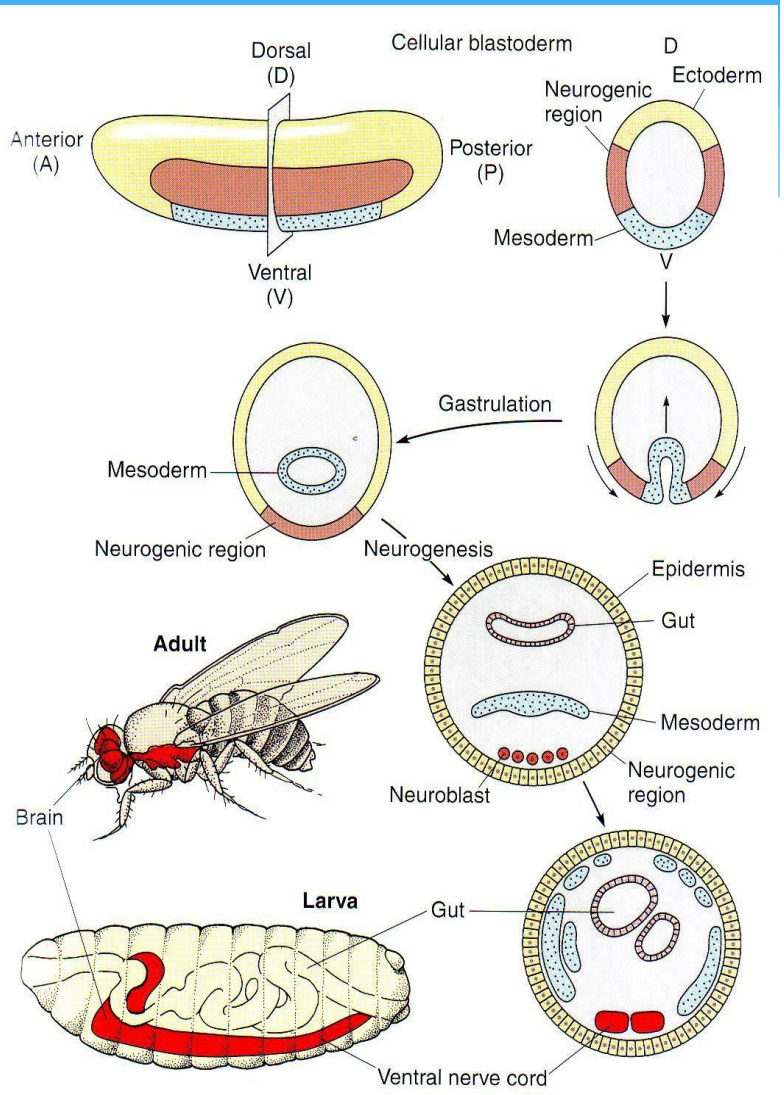
Territori presuntivi e gastrulazione in Drosophila



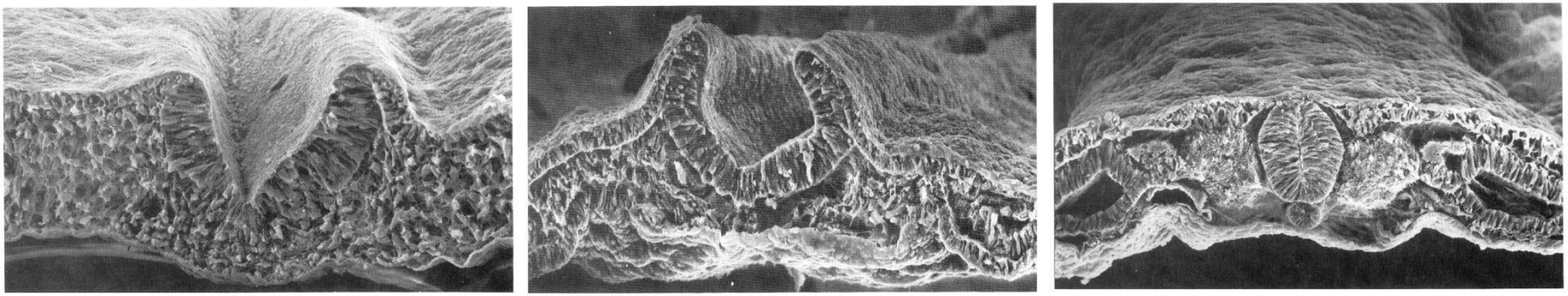


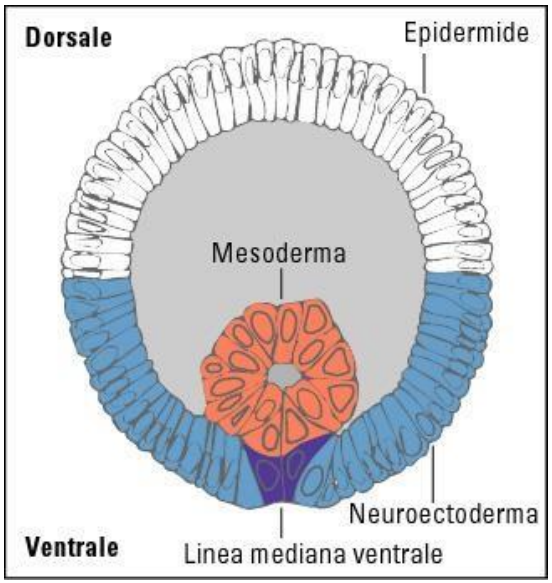
Comparazione tra SN anfibi e artropodi

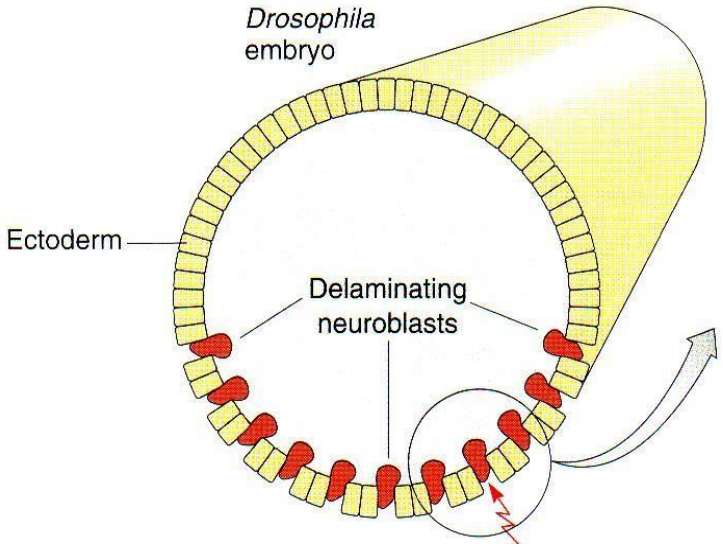




Nel vertebrato tutte le cellule del neuroepitelio diventano precursori neurali

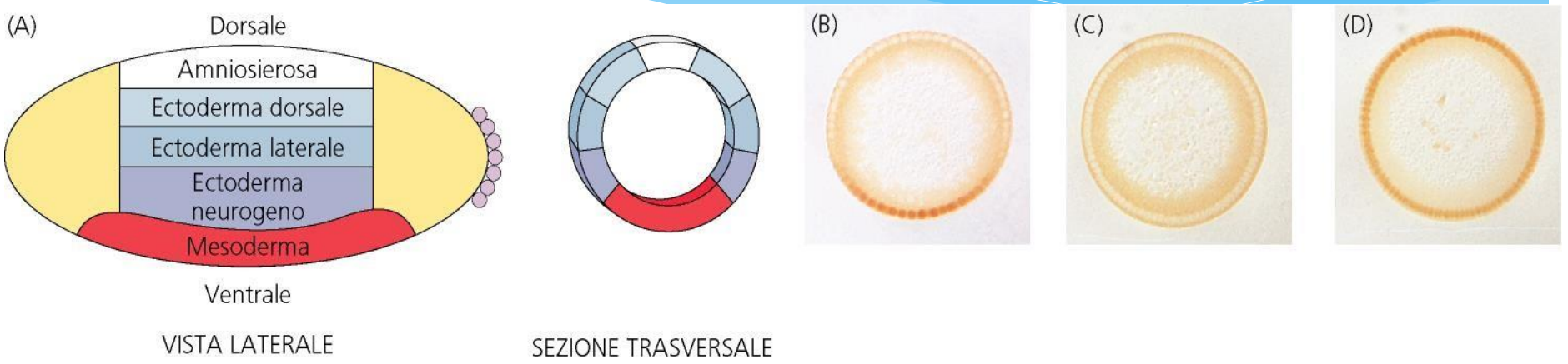






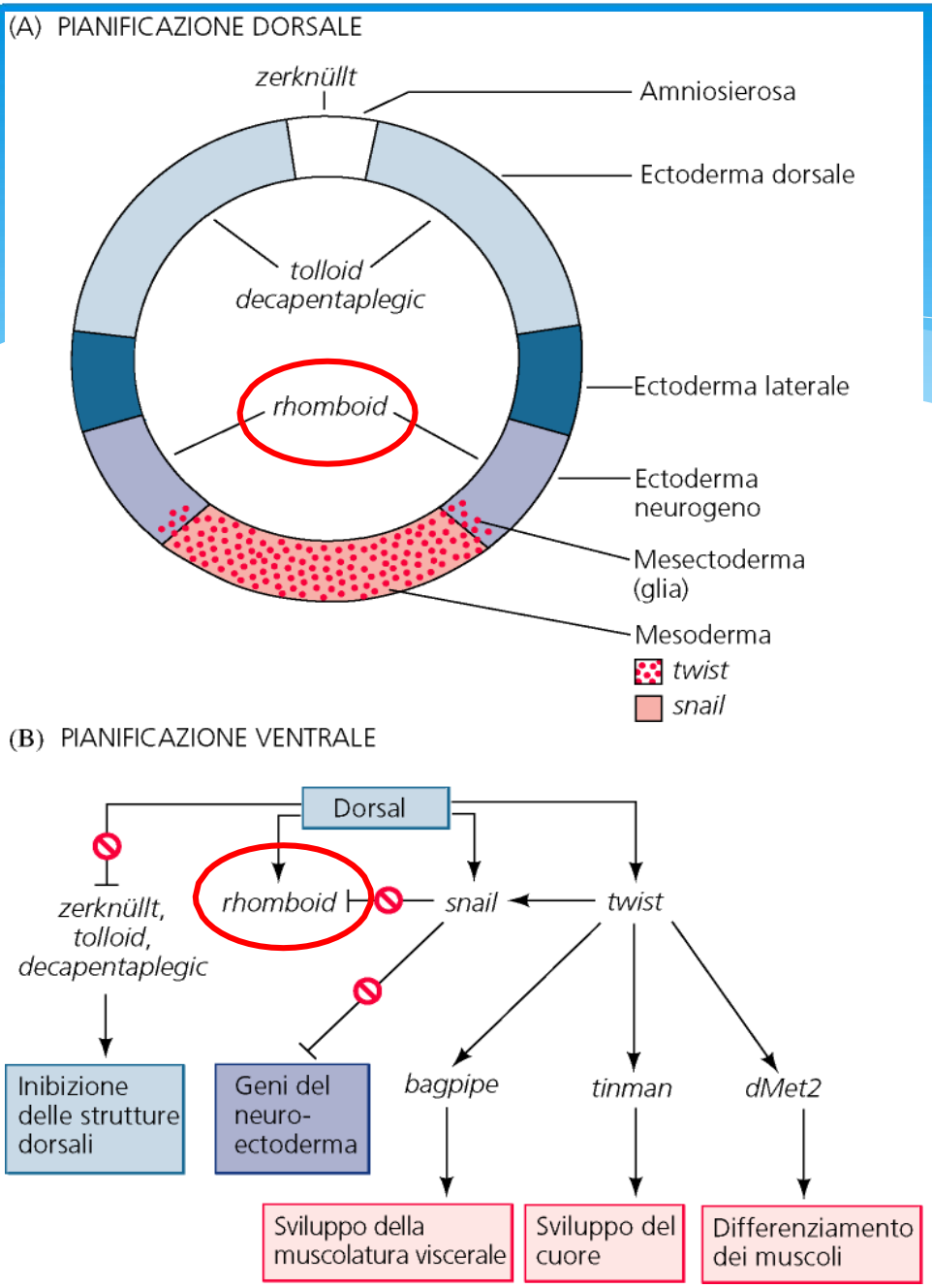
Nell'insetto , solo alcune cellule dell'epitelio neurogenico diventano veramente precursori neurali

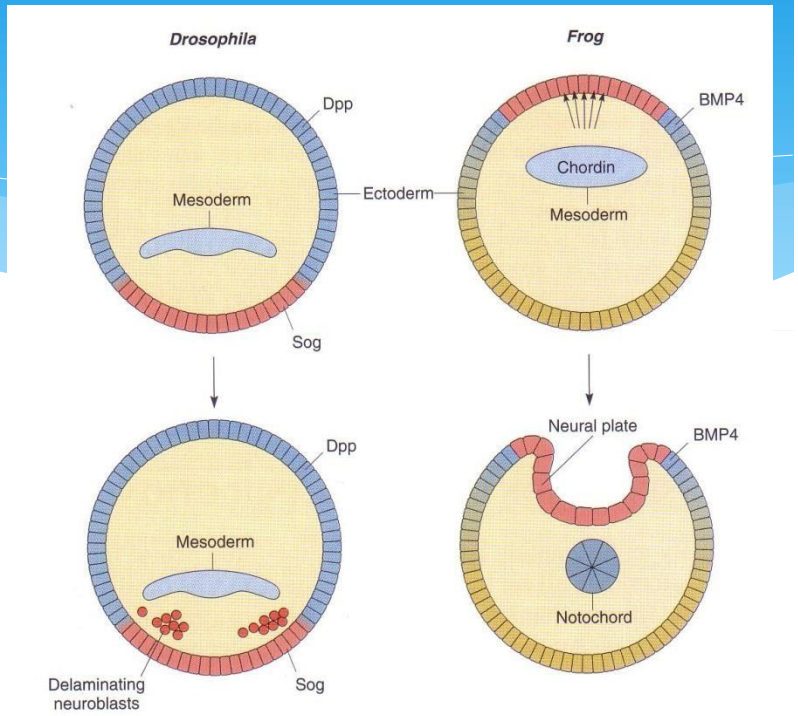
Fattori materni guidano la specificazione dei territori ventrali



Dorsal è il gene ad effetto materno responsabile della definizione dell'asse dorso ventrale di Drosophila

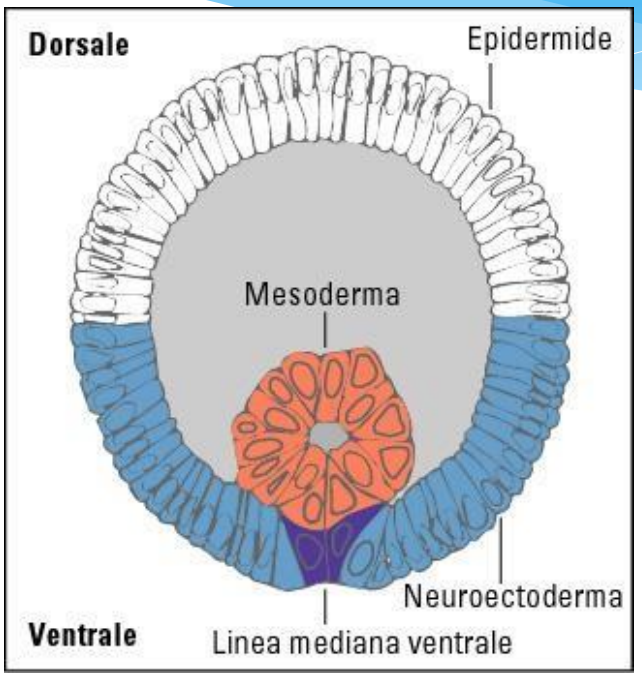
Relazione tra SN Vertebrati e Invertebrati





Sog (short gastrulation) omologo di Cordina dei vertebrati

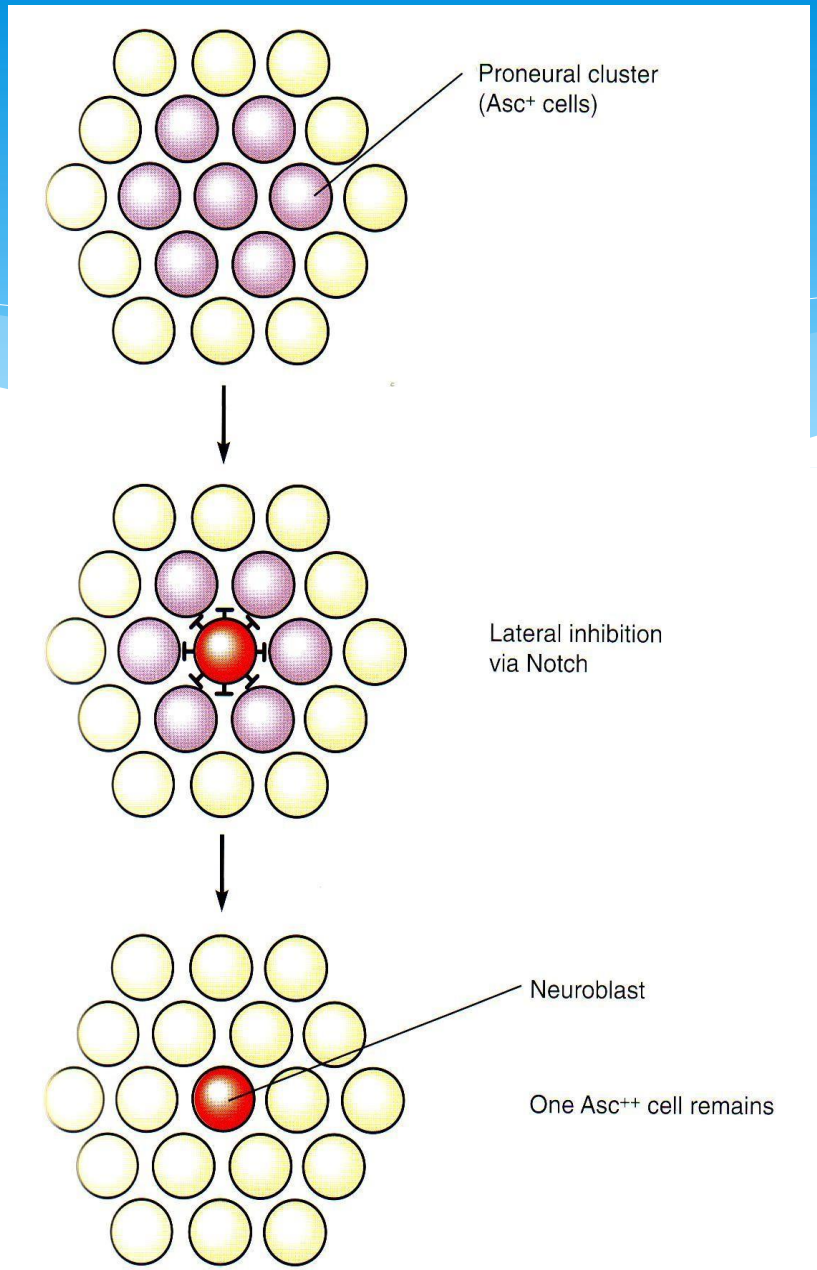
Decapentaplegic omologo di TgfB



rhomboid

complesso *achete-scute*

- Il complesso achaete –scute è comprende geni che codificano per fattori di trascrizione HLH
- Funzionano come eterodimeri, quando in presenza di partner attivi
- Sono espressi all'interno di clusters cellulari detti *clusters pro-neurali*



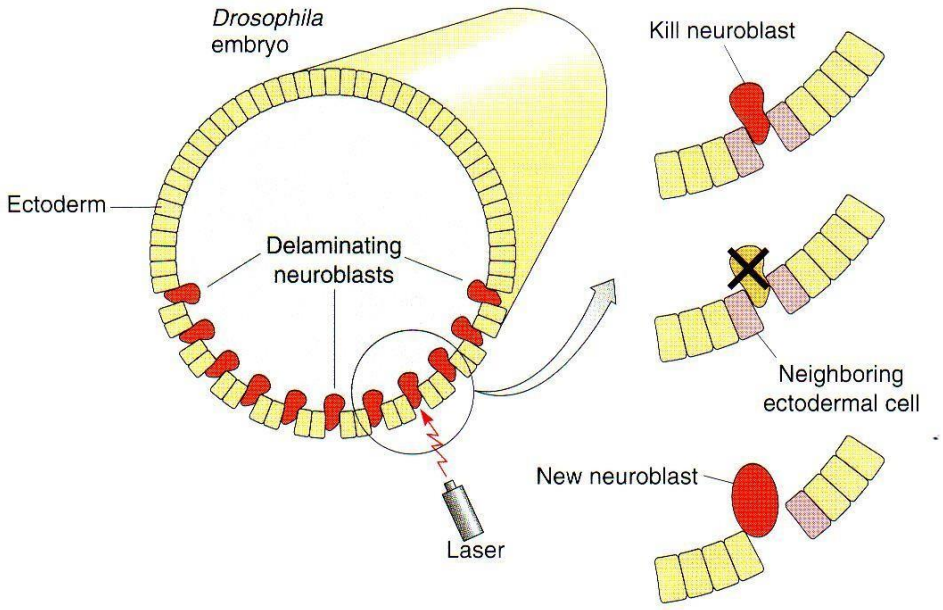
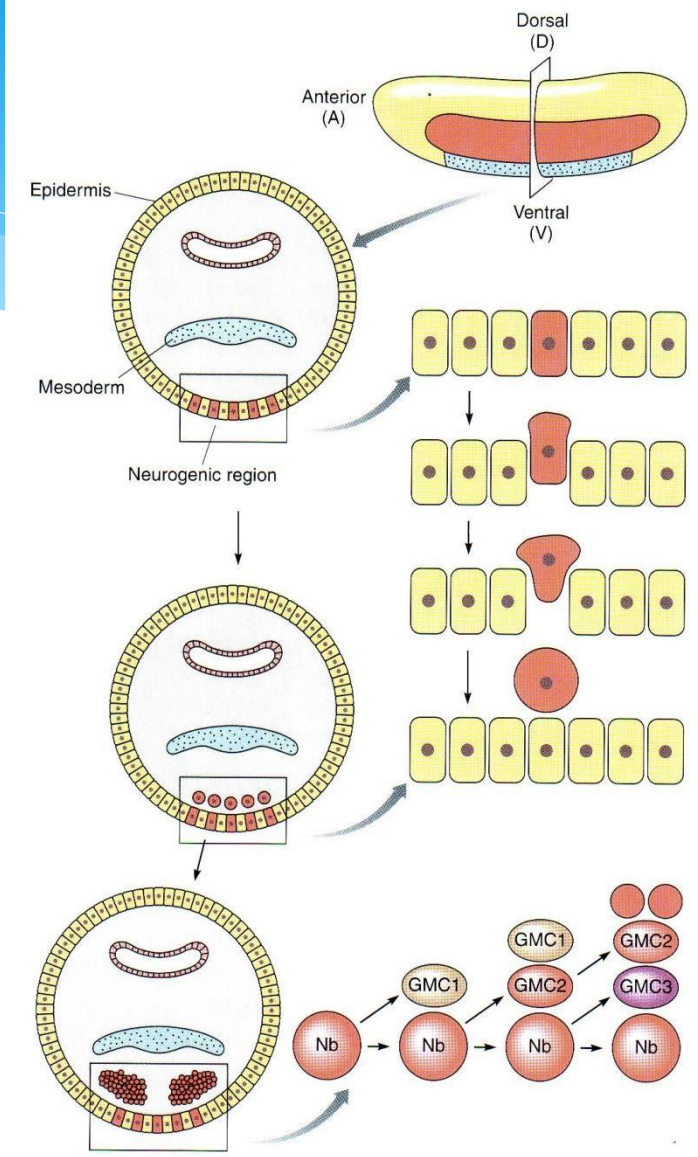
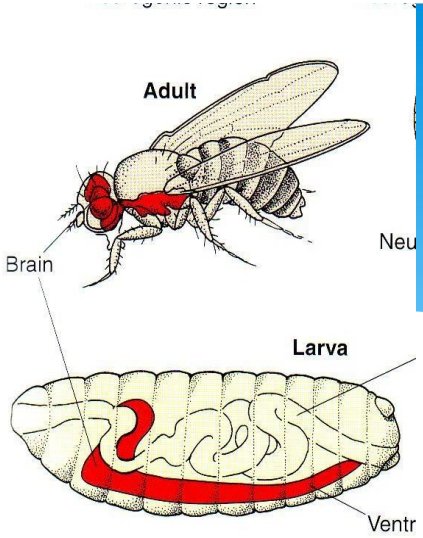


Fig. 1.26 Ablation of the delaminating neuroblast with a laser microbeam directed to the ventral neurogenic region of the fly embryo causes a neighbor-

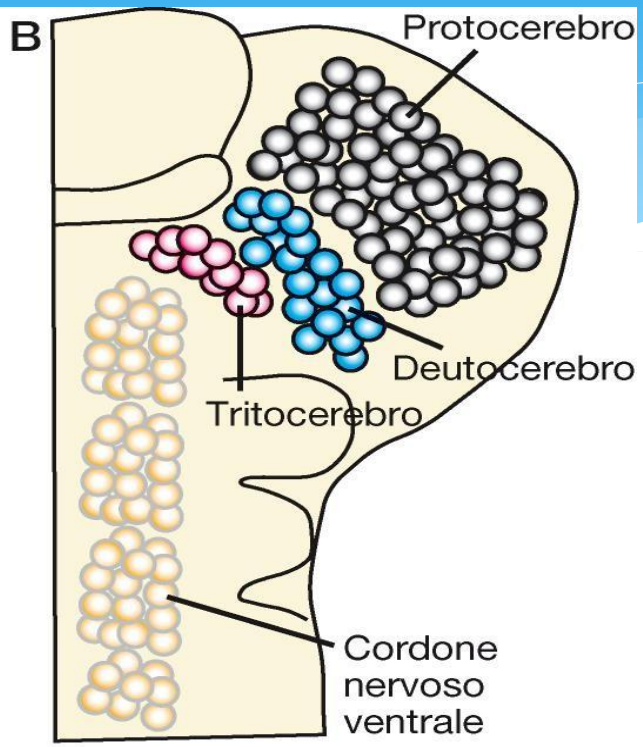


Neuroblasto mediano

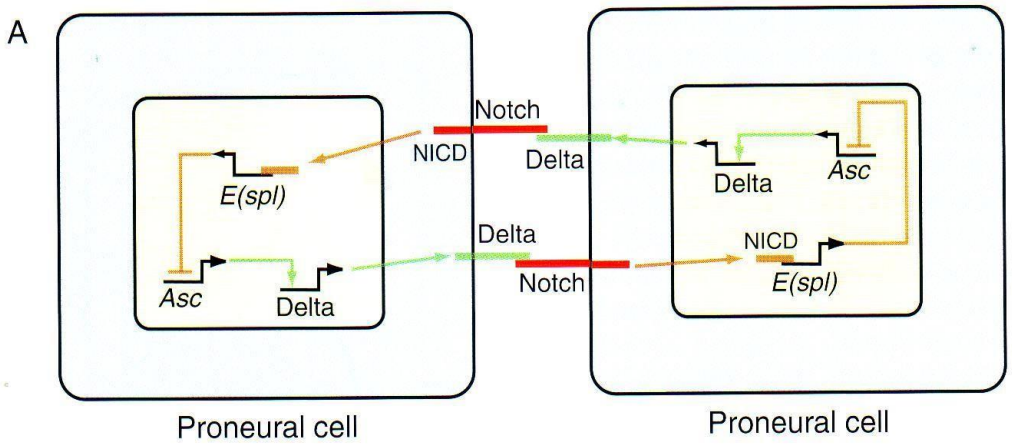
Il cordone nervoso è costituito da strutture gangliari

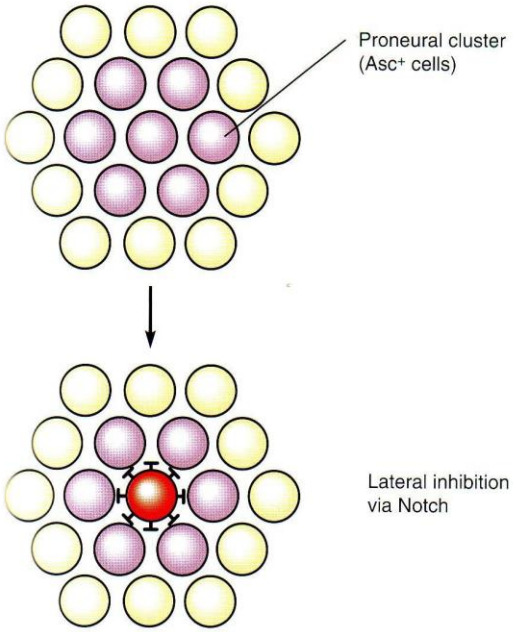






Meccanismo di inibizione laterale

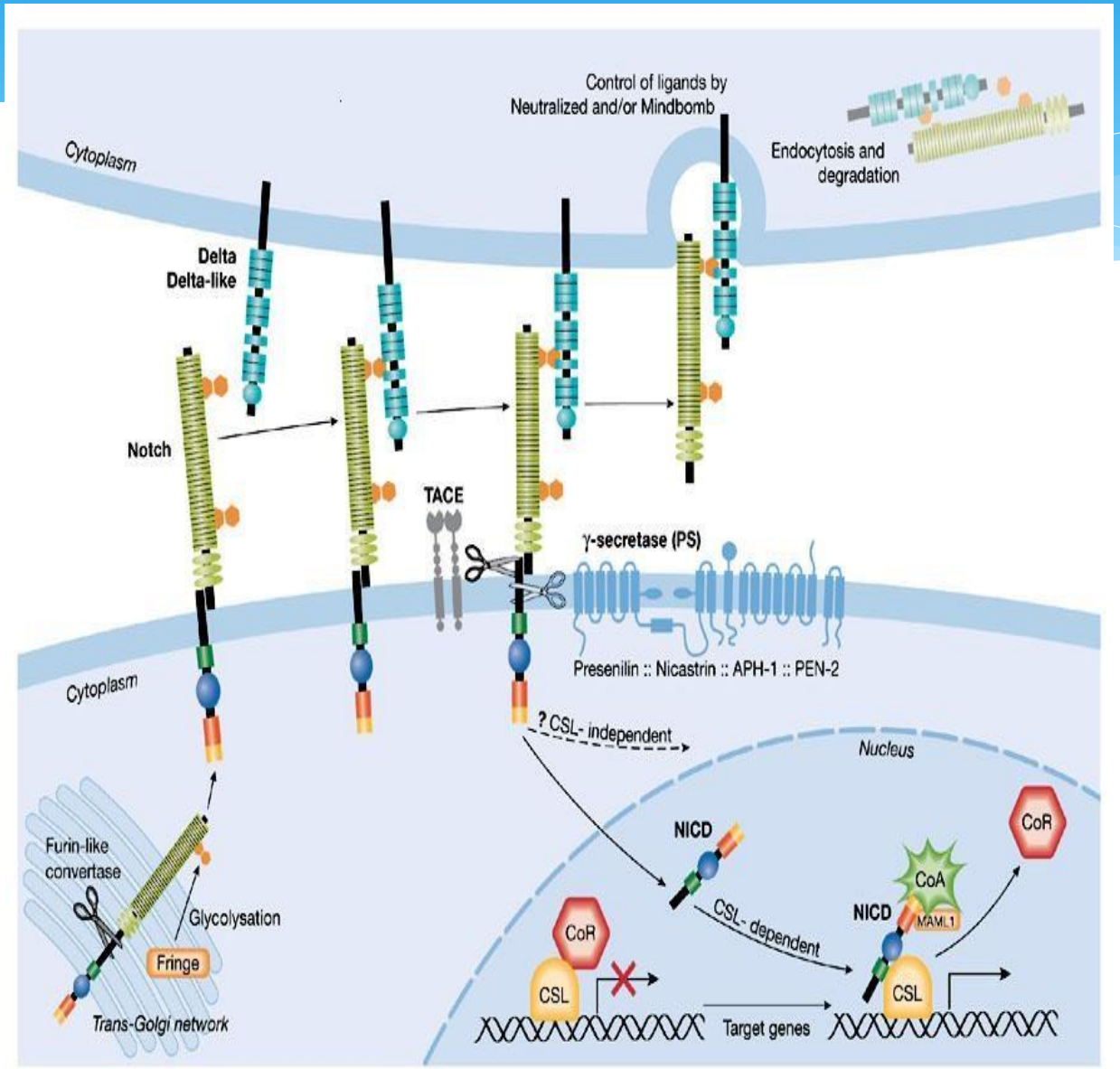


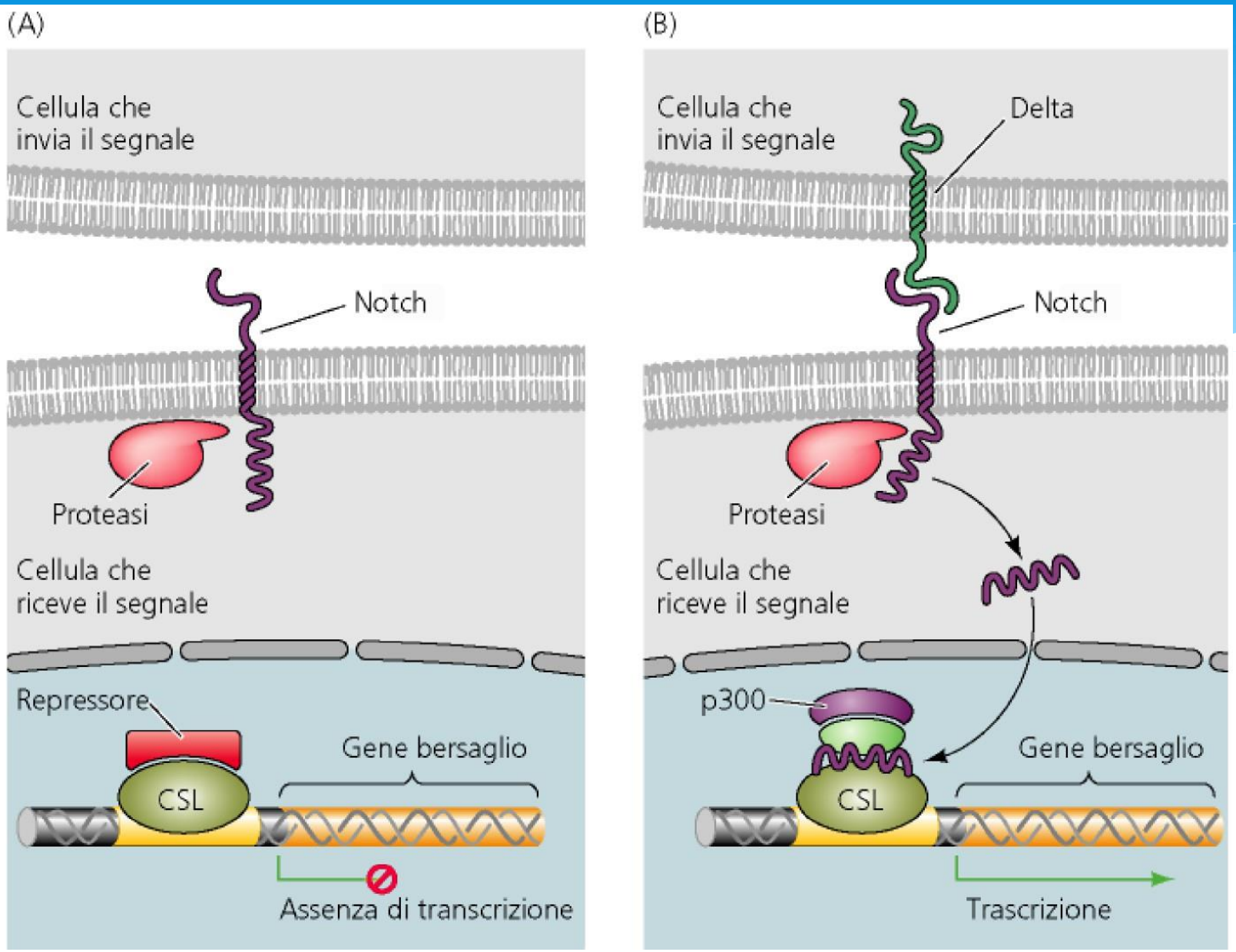


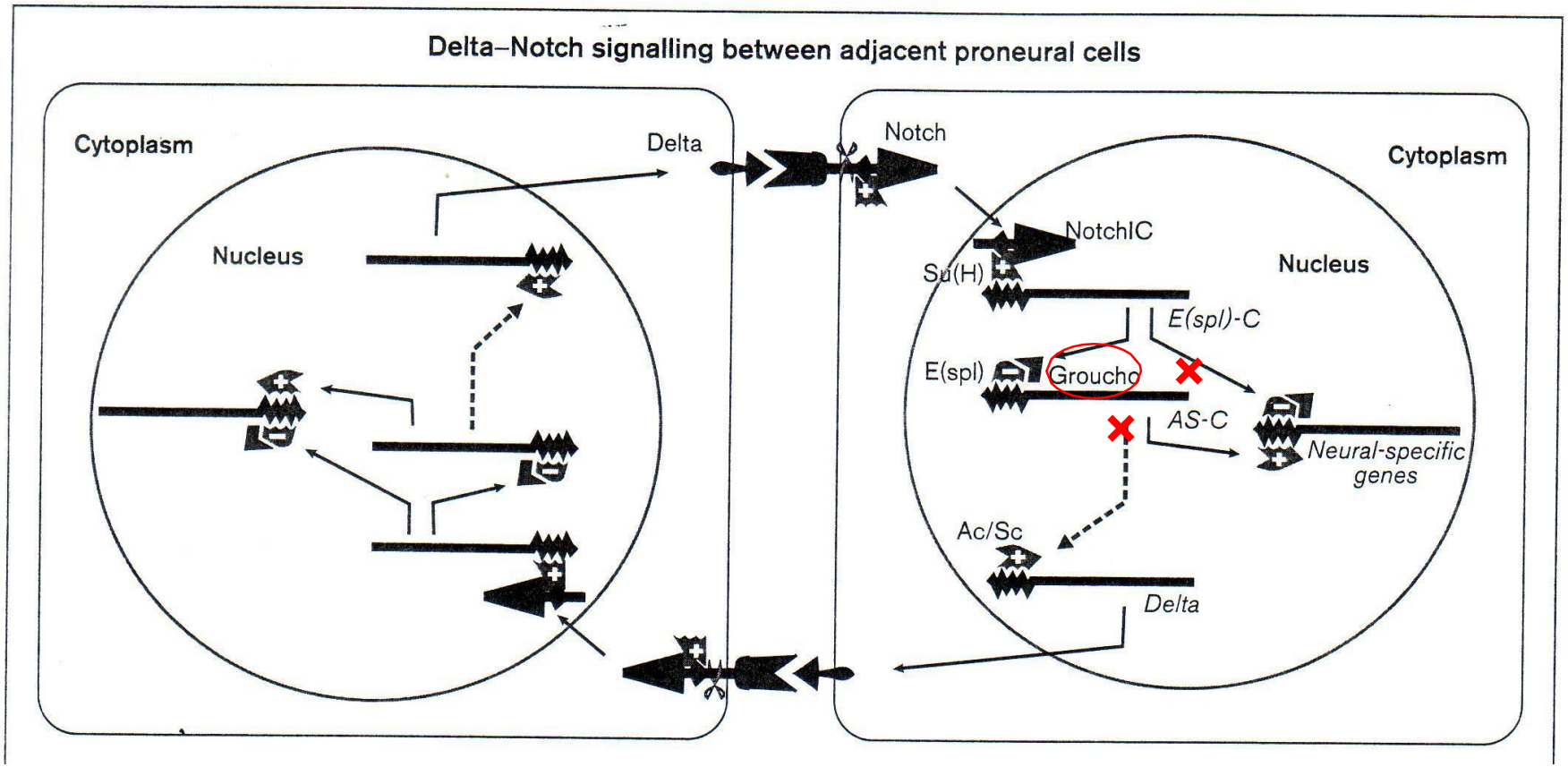
Tutte le cellule del cluster pro-neurale esprimono il sistema Delta/Notch

Il sistema Delta/Notch tiene a freno la via neurogenica

La via Delta/Notch determina la regolazione di Enhancer of split inibitore dei geni neurogenici

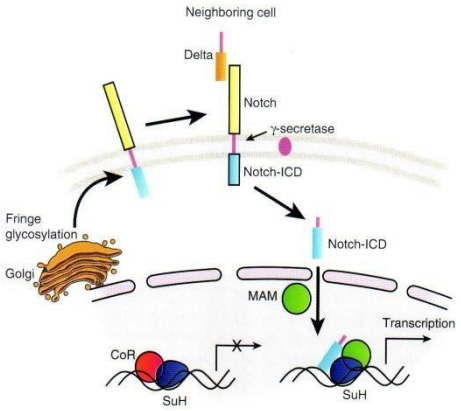



(A)
Cellula che
invia il segnale
Notch
Proteasi
Cellula che
riceve il segnale
Repressore
CSL
Gene bersaglio
Assenza di transcrizione
(B)
Cellula che
invia il segnale
Delta
Notch
Proteasi
Cellula che
riceve il segnale
p300
CSL
Gene bersaglio
Trascrizione



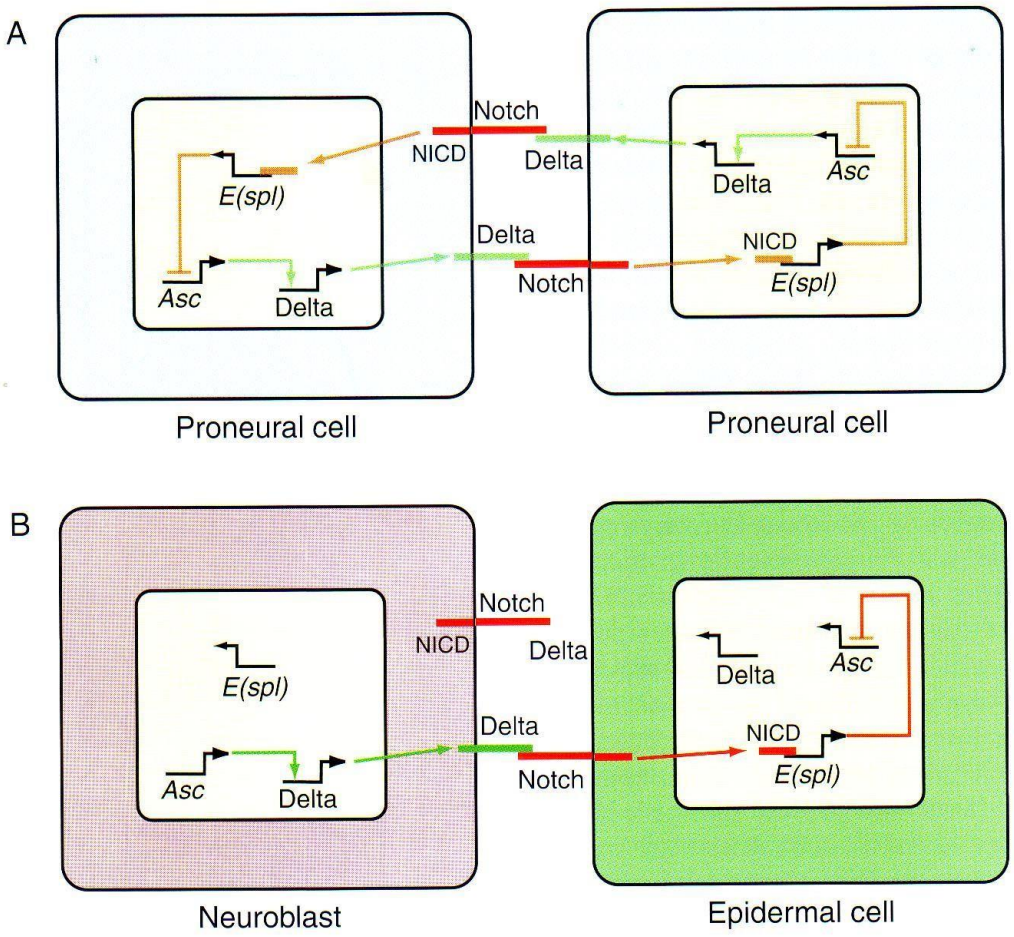
E (spl) è un fattore bHLH che è in grado di funzionare come omodimero.
Funziona da repressore genico reclutando il co-repressore Groucho

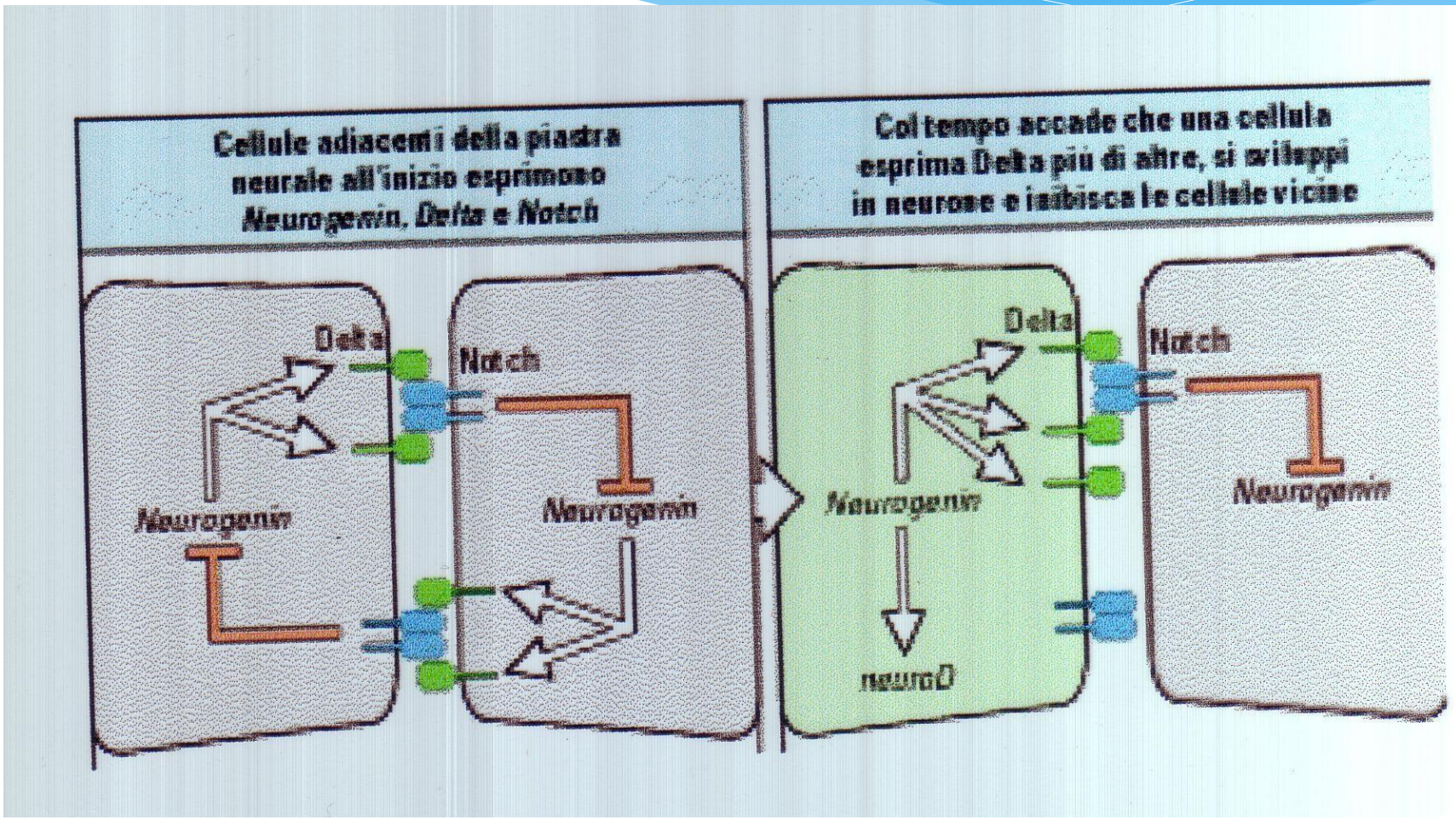
Meccanismo di inibizione laterale

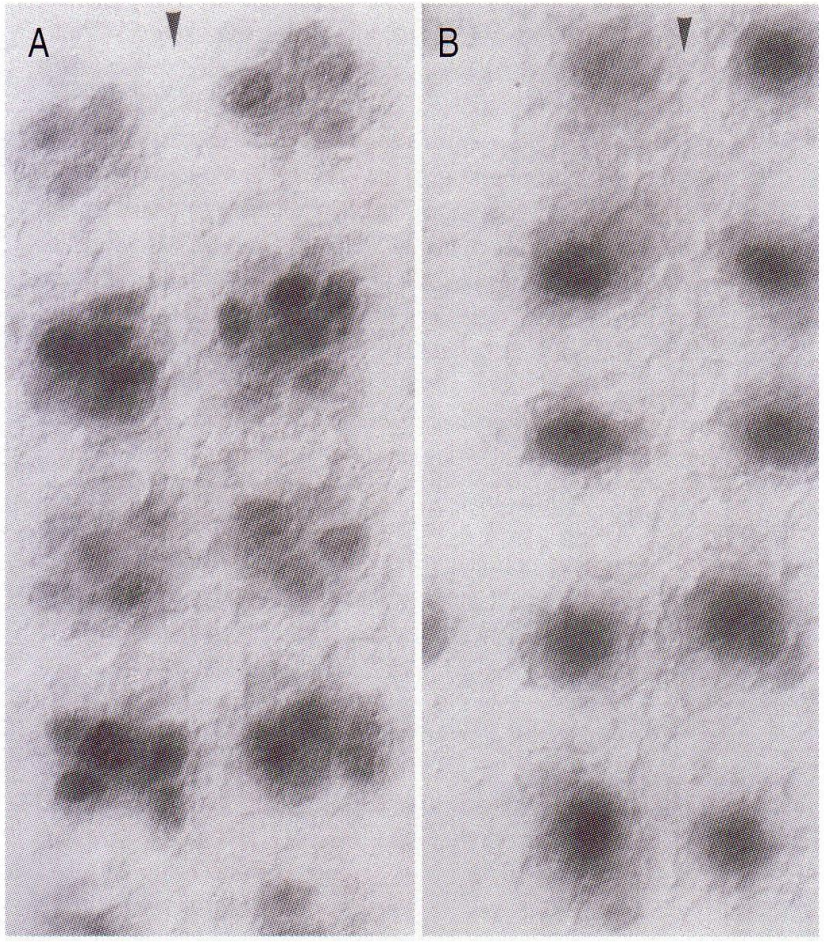


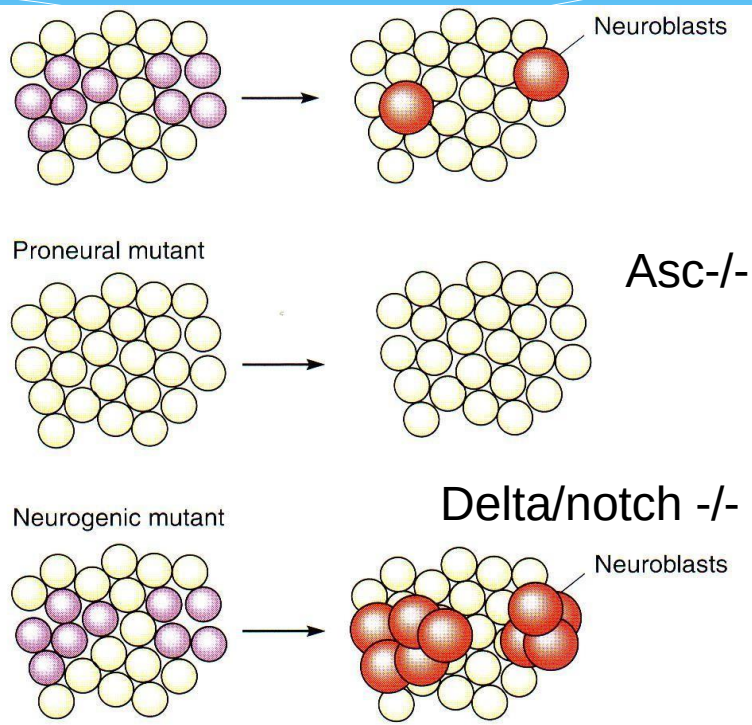
Notch → E(spl)

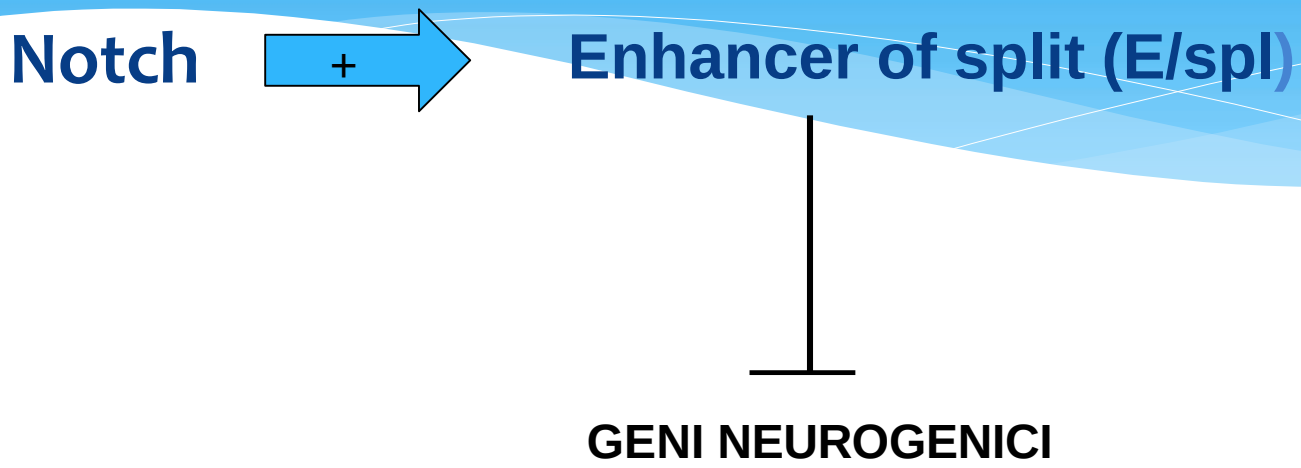
ACS → Delta

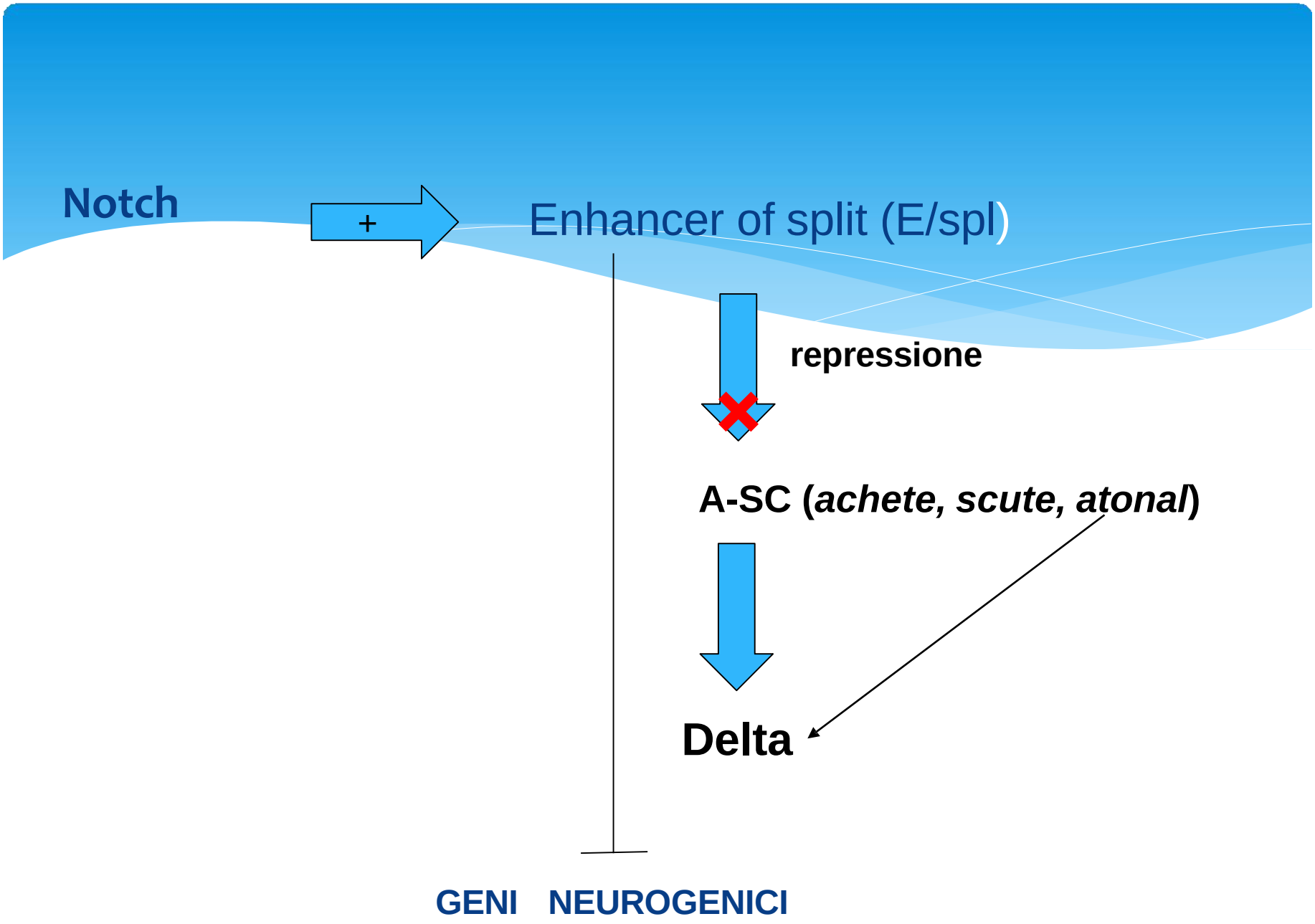


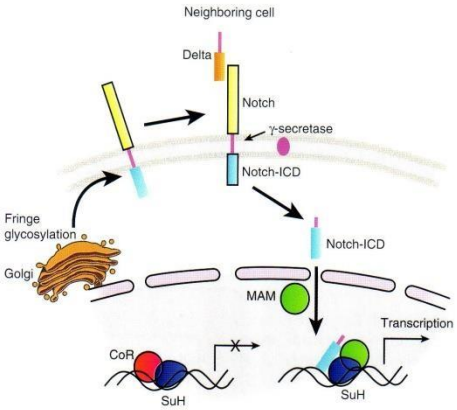

Cellule adiacenti della piastra neurale all'inizio esprimono Neurogenin, Delta e Notch
Col tempo accade che una cellula esprima Delta più di altre, si sviluppi in neurone e inibisca le cellule vicine
Delta
Notch
Neurogenin
Neurogenin
Delta
Notch
Neurogenin
neuroD


A
B


Neuroblasts
Proneural mutant
Asc-/-
Neurogenic mutant
Delta/notch -/-
Neuroblasts

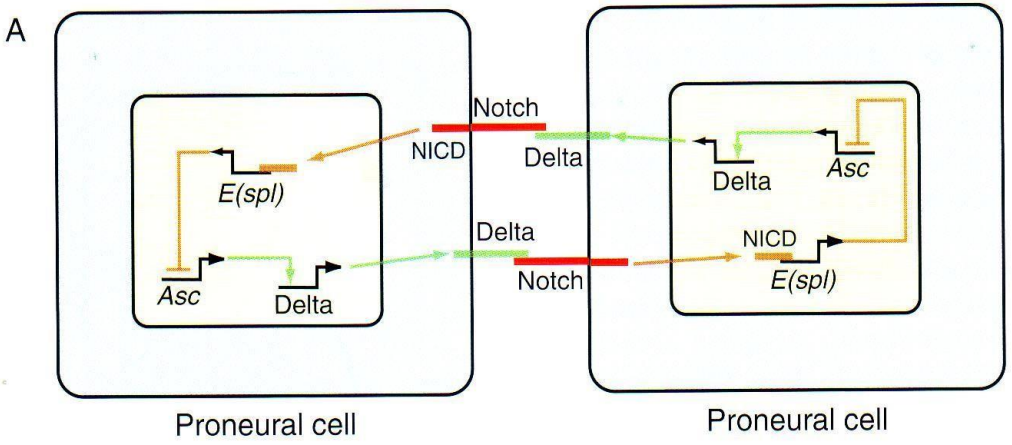

Notch
+
Enhancer of split (E/spl)
GENI NEUROGENICI

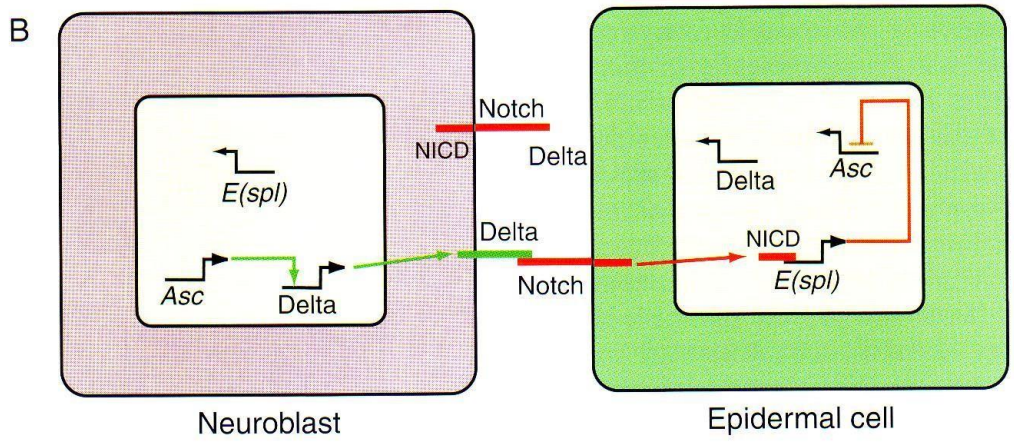

Notch
+
Enhancer of split (E/spl)
repressione
A-SC (*achete, scute, atonal*)
Delta
GENI NEUROGENICI



Notch → E(spl)

ACS → Delta

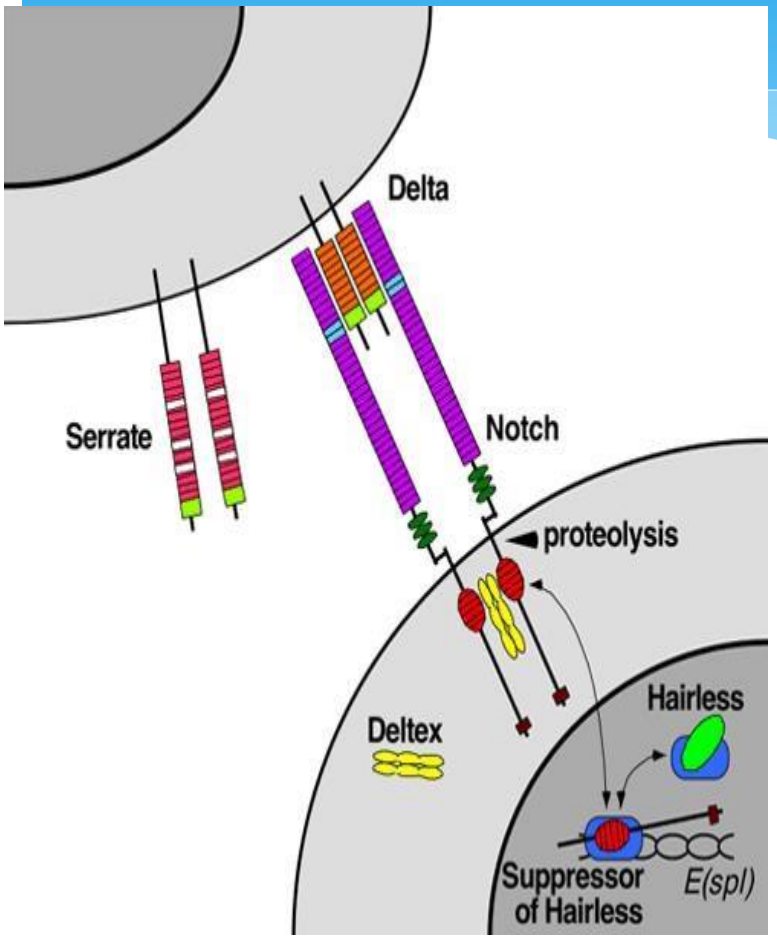




L’interferenza delle via TgfB è comune in anfibio e insetto

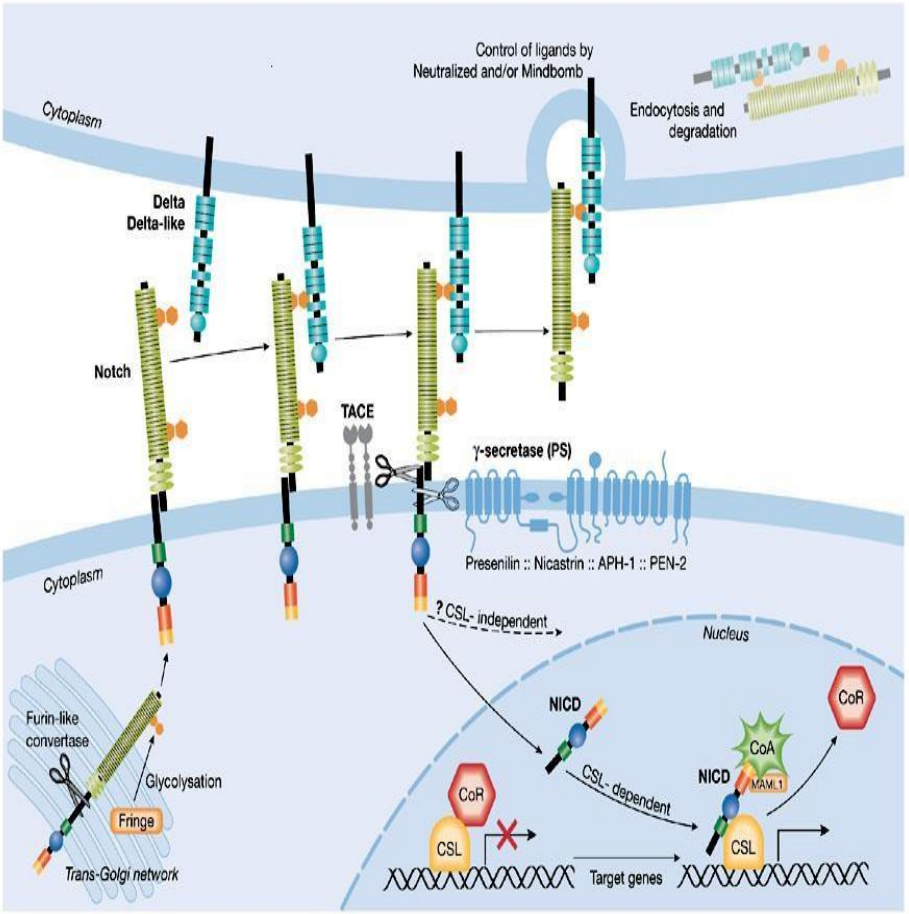
Il sistema Delta-Notch è presente nel vertebrato????

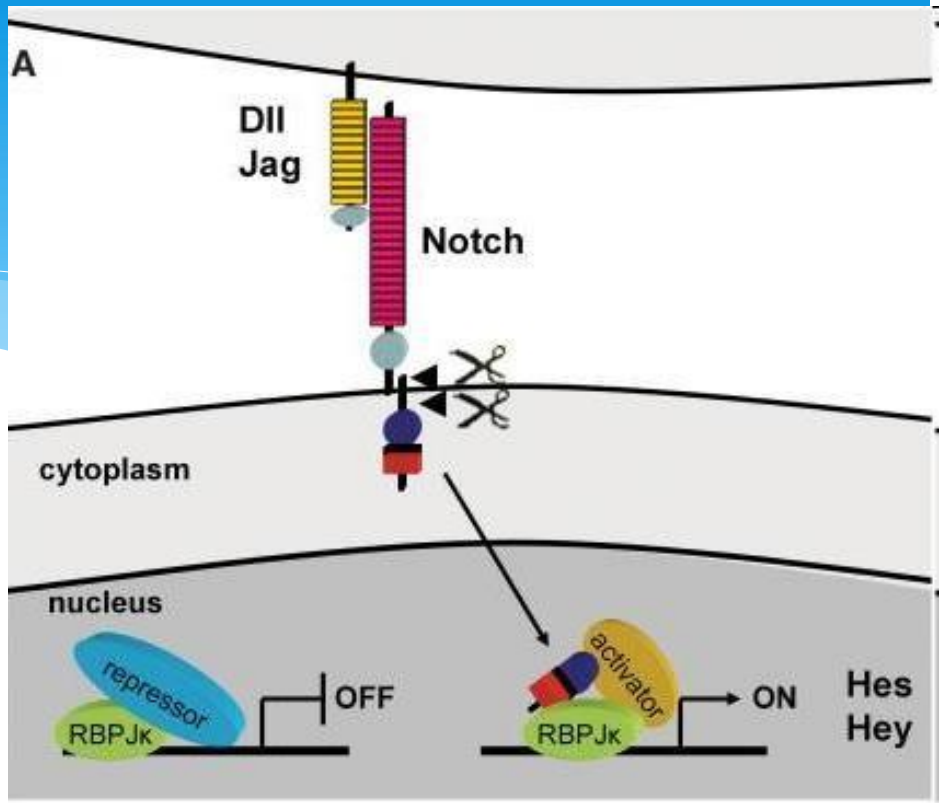
Ligandi di Notch

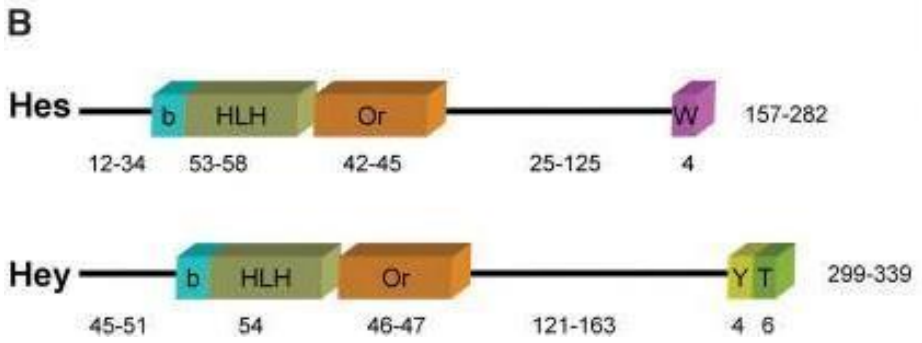


1. Delta
2. Serrate (omologo di Delta)

3. Nel vertebrato Delta-1 e Jagged (omologo di Serrate, espresso in aree ristrette della zona ventricolare)


Control of ligands by
Neutralized and/or Mindbomb
Endocytosis and
degradation
Cytoplasm
Delta
Delta-like
Notch
TACE
γ-secretase (PS)
Presenilin :: Nicastrin :: APH-1 :: PEN-2
Cytoplasm
? CSL- independent
Nucleus
Furin-like
convertase
Glycolysation
Fringe
Trans-Golgi network
NICD
CSL- dependent
CoR
CoA
NICD
MAML1
CoR
CSL
CSL
Target genes


A
Dll
Jag
Notch
cytoplasm
nucleus
repressor
RBPJκ
OFF
activator
RBPJκ
ON
Hes
Hey


B
Hes
b
HLH
Or
W
157-282
12-34
53-58
42-45
25-125
4
Hey
b
HLH
Or
Y T
299-339
45-51
54
46-47
121-163
4 6

HES Family: gli omologhi di E(spl)

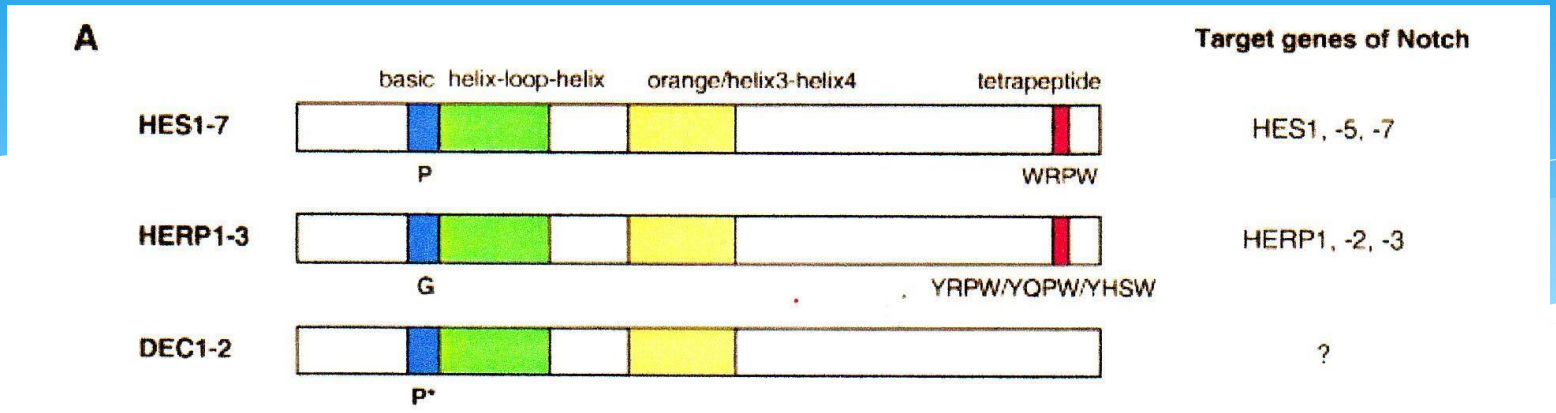
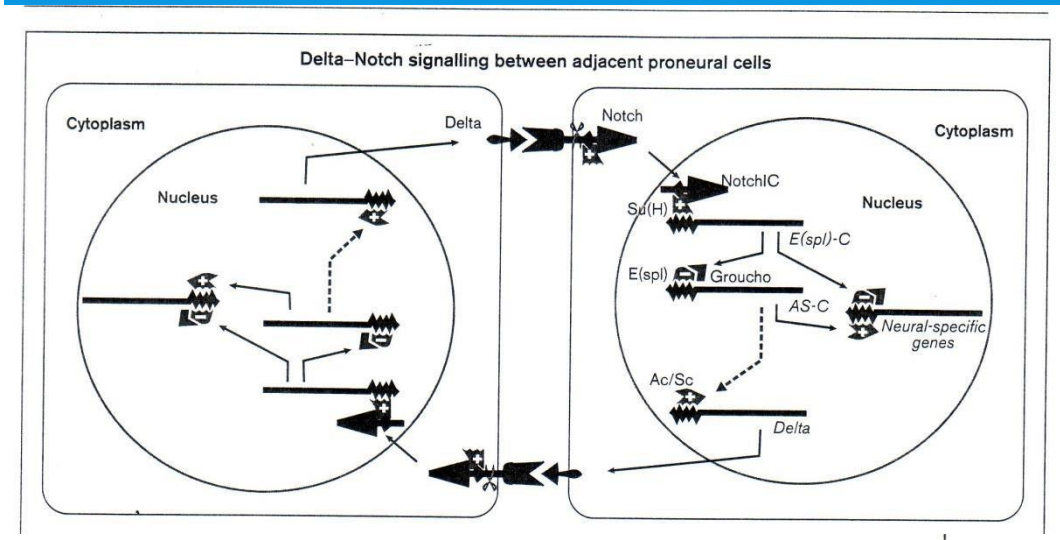


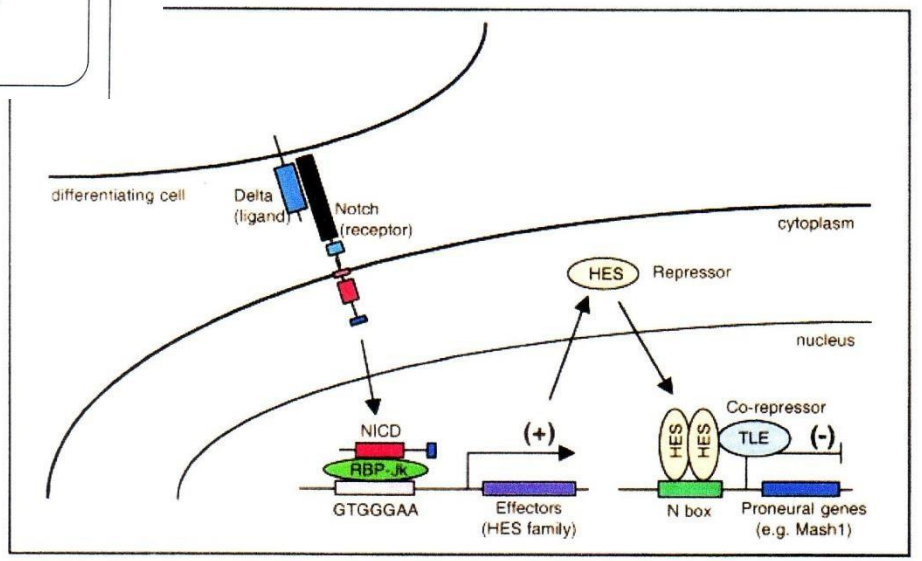
TABLE 2B. Consensus binding site HLH transcription factors

Classification		Consensus	Examples	
Class A	Attivatori	CANCTG	CACCTG, CAGCTG	MyoD, Mash-1
Class B		CANGTG	CACGTG, CATGTG	Myc, Max
Class C	Repressori	CACGNG	CACGCG, CACGAG	
E box		CANNTG	CACCTG, CAGCTG, CACGTG, CATGTG	
N box		CACNAG	CACGAG, CACAAG	

Class A and B are subtypes of E box. Class C and N box are mutually overlapping.

Comprende geni HES, HERP e Hey





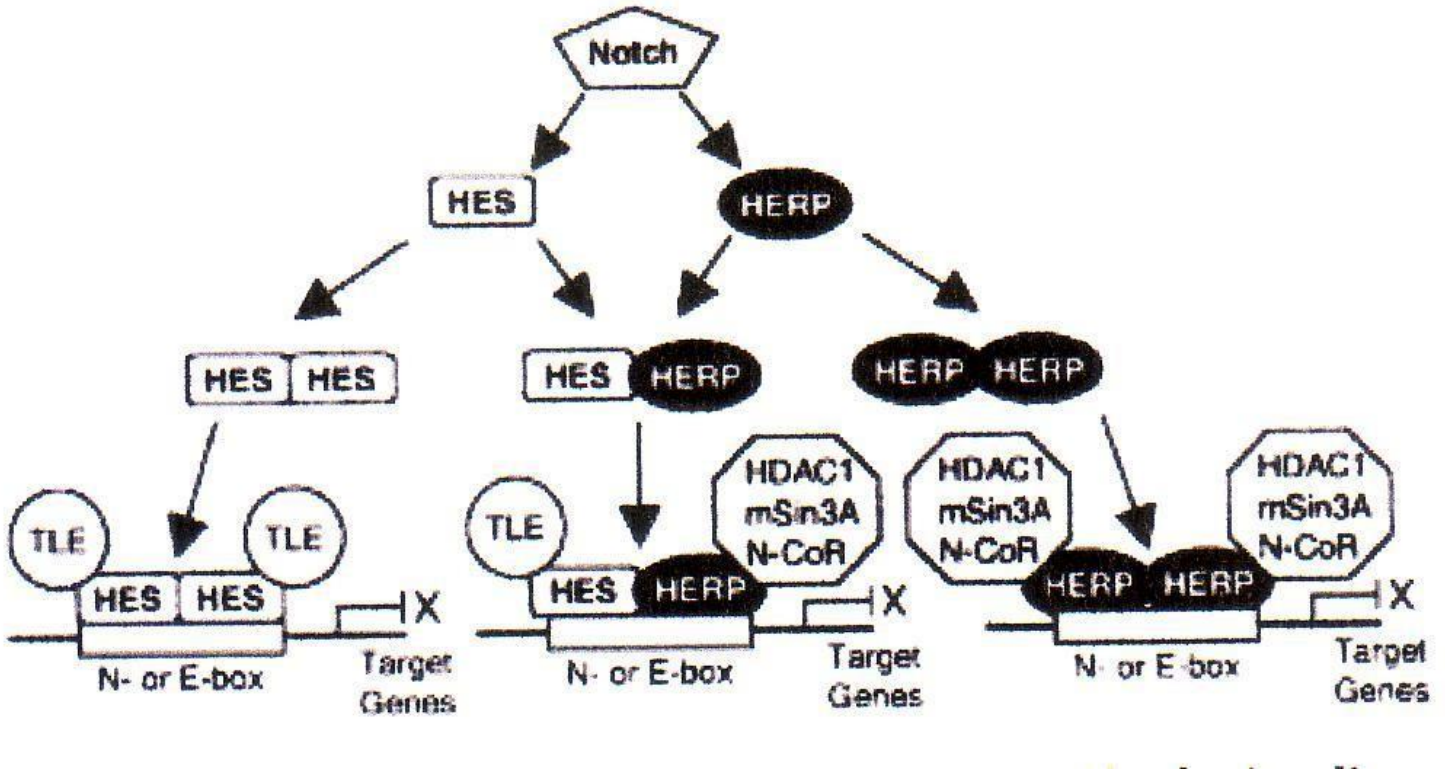
Meccanismi di repressione genica

1. Hes può omodimerizzare

Recluta un omologo di Groucho (un co-repressore che viene reclutato da E (spl)) che a sua volta recluta una istone deacetilasi

2. Repressione passiva: E(spl) eterodimerizza con E47 (bHLH) sottraendolo all'interazione con geni neurogenici

3. Dominio orange recluta un co-repressore diverso da Groucho



I geni Hes e Herp possono omodimerizzare o eterodimerizzare

Modificazione epigenetica del DNA

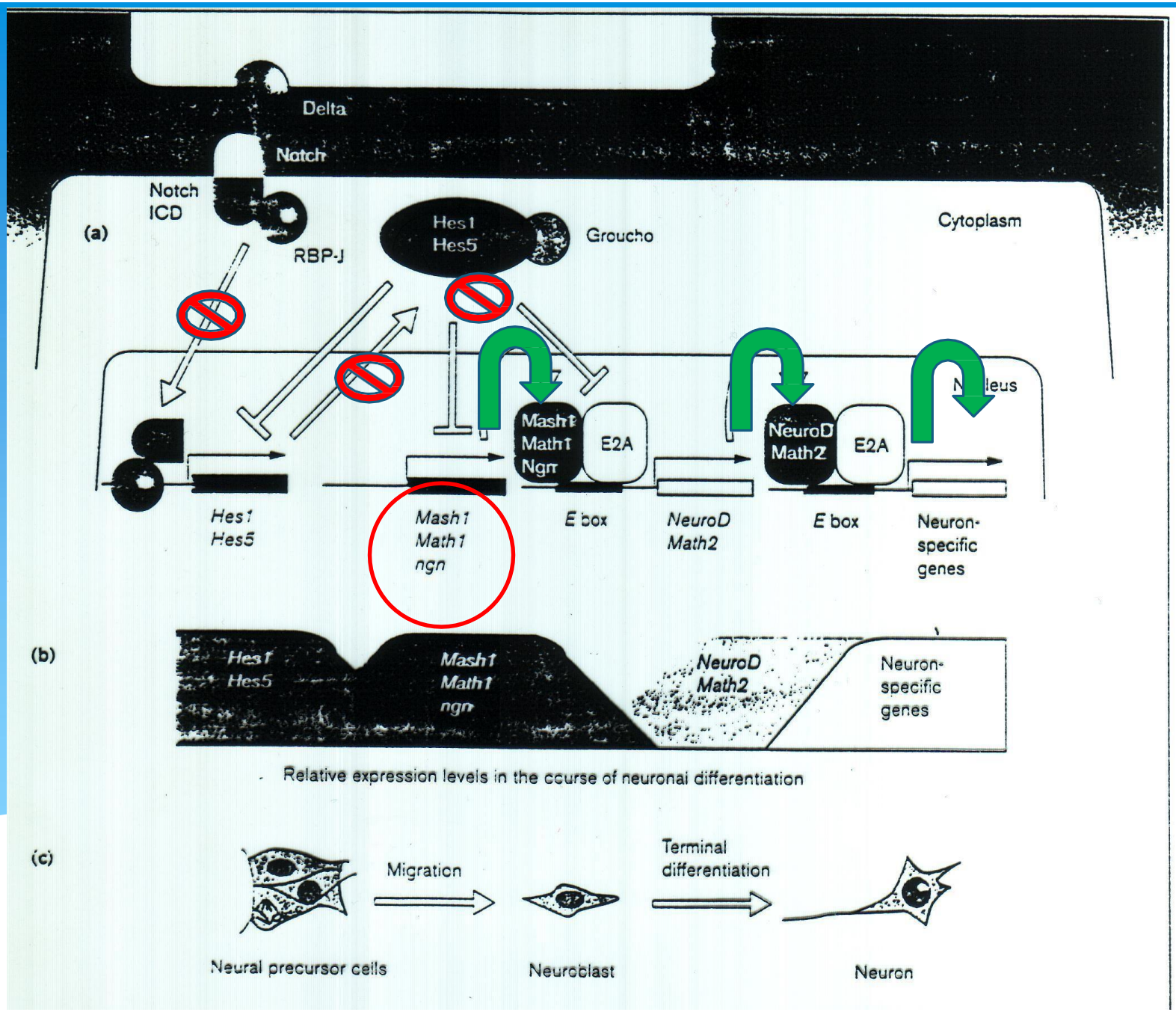
Phenotypes of *Hes* or *Hey* gene deficient mice

	Notch regulated	Mouse knockout phenotype	References
Hes1	Yes	Neurulation defects, premature differentiation of neural progenitor cells	(120–122)
		Eye and inner ear defects	(123–125)
		Pancreas defects and defective endocrine differentiation	(126)
		Disturbed T-cell differentiation, lack of thymus	(127)
Hes3	No	Viable, fertile	(128)
Hes5	Yes	Viable, fertile	(35,121)
		Eye and inner ear defects	(129,104)
		Elevated myelin levels in central nervous system	(117)
Hes6	No	Viable, fertile	(24)
Hes7	Yes	Somitogenesis defects	(108)
Hes1/5		Enhancement of Hes1$^{-/-}$ phenotype	(35,121,125,130)
		Defects in cranial and spinal nerves	(131)
Hes1/3		Missing midbrain and anterior hindbrain due to premature neuronal differentiation	(128)
Hes1/3/5		More severe than Hes1/5 loss	(125)
Hey1	Yes	Viable, fertile	(132,133)
Hey2	Yes	Congenital heart defects	(134–138)
		Decreased arterial neointima formation	(87)
HeyL	Yes	Viable, fertile	(47)
Hey1/2		Angiogenesis and arterial differentiation defects	(132,133)
Hey1/L		Congenital heart defects	(47)

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1. Aumentata espressione di Hes-1 inibisce la formazione di neuroblasti

2. KO Hes-1 si formano neuroni prematuri (anticipo del processo maturativo)


Delta
Notch
Notch ICD
(a)
RBP-J
Hes1 Hes5
Groucho
Cytoplasm
Mash1 Math1 Ngn
E2A
NeuroD Math2
E2A
Hes1 Hes5
Mash1 Math1 ngn
E box
NeuroD Math2
E box
Neuron-specific genes
(b)
Hes1 Hes5
Mash1 Math1 ngn
NeuroD Math2
Neuron-specific genes
Relative expression levels in the course of neuronal differentiation
(c)
Migration
Terminal differentiation
Neural precursor cells
Neuroblast
Neuron

* **Geni neurogenici primari:**
  Mash1, Math1, Neurogenin determinano il passaggio da precursore neurale a neuroblasto (HLH attivatori di geni neurogenici secondari)

Geni neurogenici 2:

Mash2, Math2, NeuroD determinano il passaggio da neuroblasto a neurone

(HLH attivatori di geni neurospecifici)

Geni Neurospecifici: A valle dei geni neurogenici di classe 2 ci sono i geni neurospecifici che caratterizzano l'avvio della fase differenziativa (es. NCAM e Neurofilamenti)

Sistema Delta-Notch: quale è la differenza tra Invertebrati e Vertebrati



Cellula del cluster pro-neurale

BMP/Tgf beta

Precursore neurale



Notch +

Notch -

Precursore epiteliale

Precursore neurale

Progenitore neuronale

Prog. gliale

Notch +

Precursore neurale

Notch +

Notch-

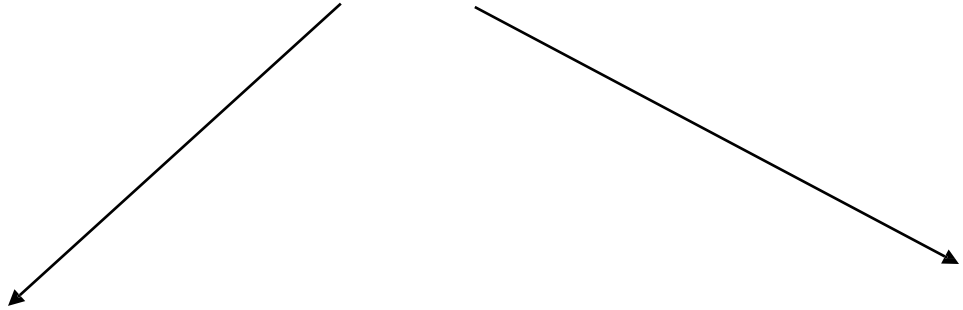
Neuroblasto

* Nel Vertebrato

Notch-1 è espresso inizialmente da tutte le cellule del neuroepitelio del tubo neurale

Delta-1 è espresso abbondantemente nelle cellule che smettono di proliferare che cominciano ad abbandonare lo strato germinativo

* Nel Vertebrato Notch/Delta non interviene nella scelta tra precursore epiteliale e precursore neurale
* Notch/Delta si attiva nei precursori neurali



Finchè attivo, tiene a freno l'avanzamento verso la via neuronale bloccando i geni neurospecifici

Può favorire la via gliogenica