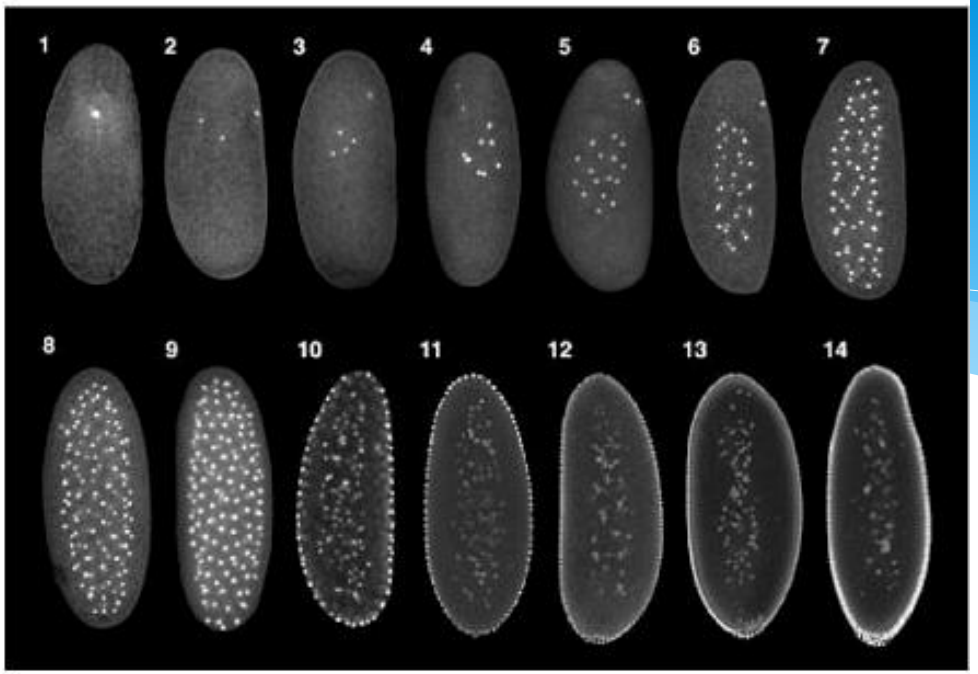
# La specificazione del sistema nervoso negli insetti

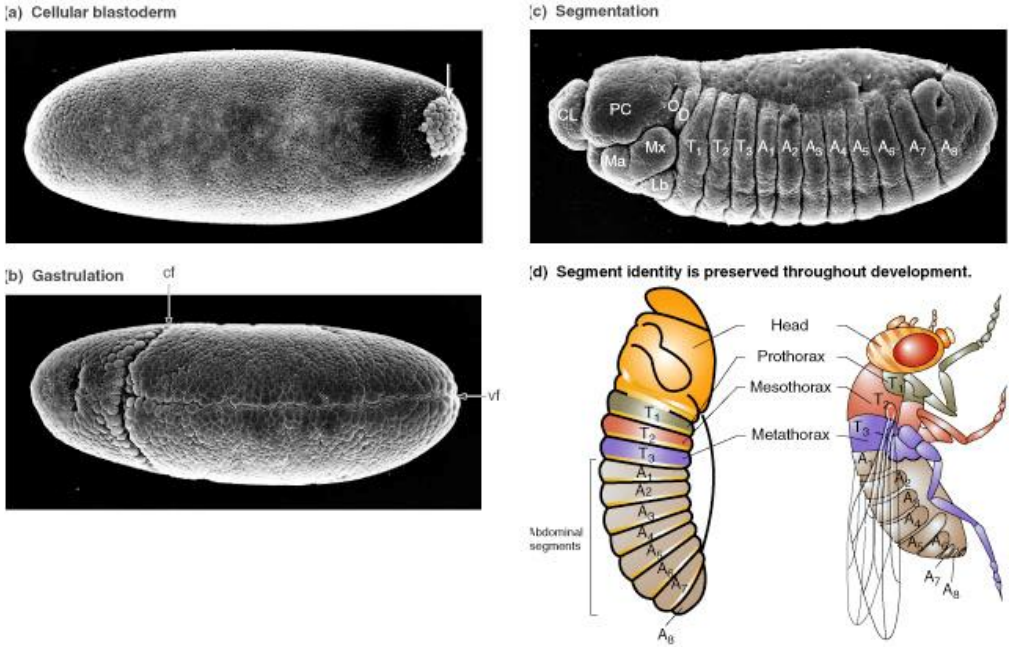
(b) Early embryonic stages in cross section



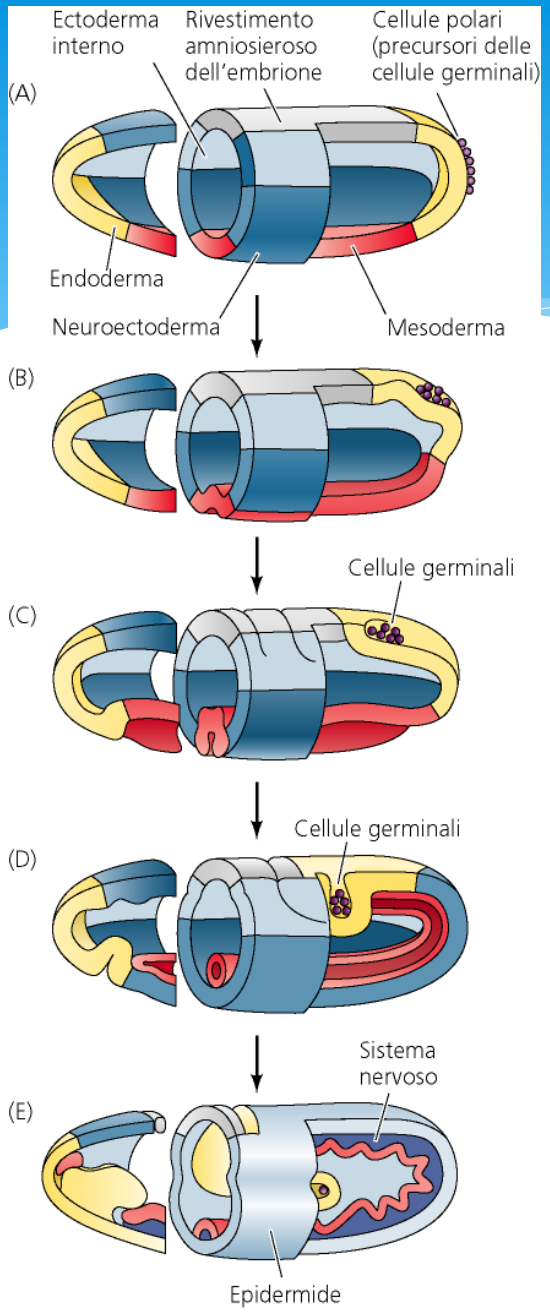

**Segmentazione**
**Meroblastica superficiale**

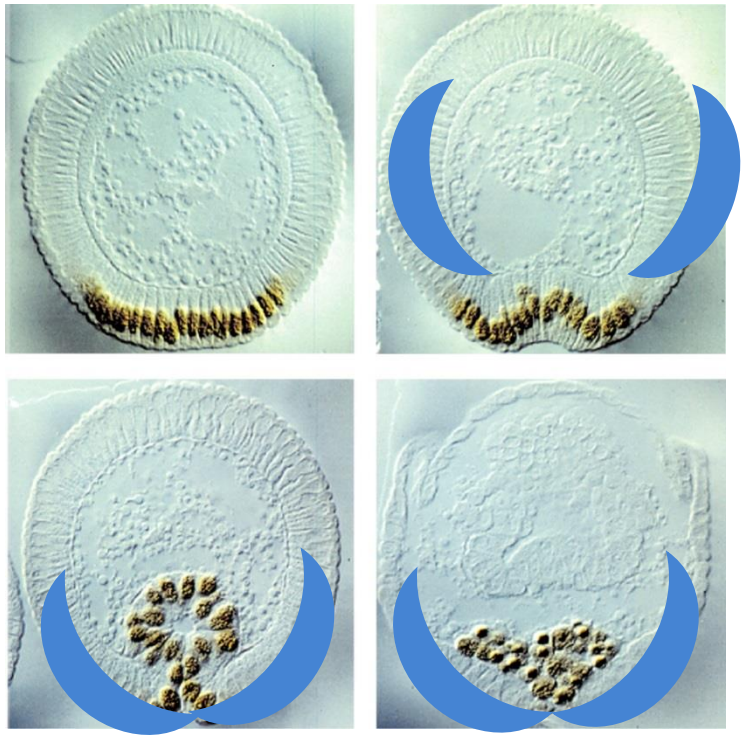
Blastoderma sinciziale
Blastoderma cellulare (dal 14° ciclo mitotico)

**gastrulazione**

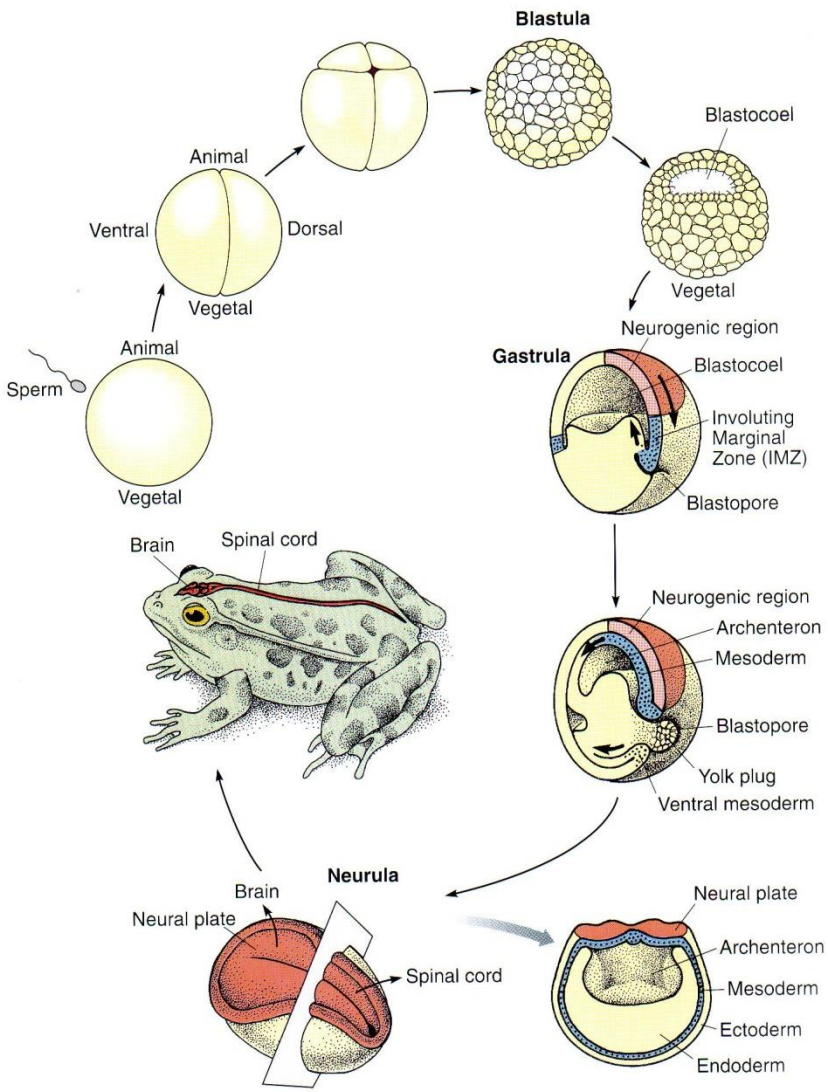


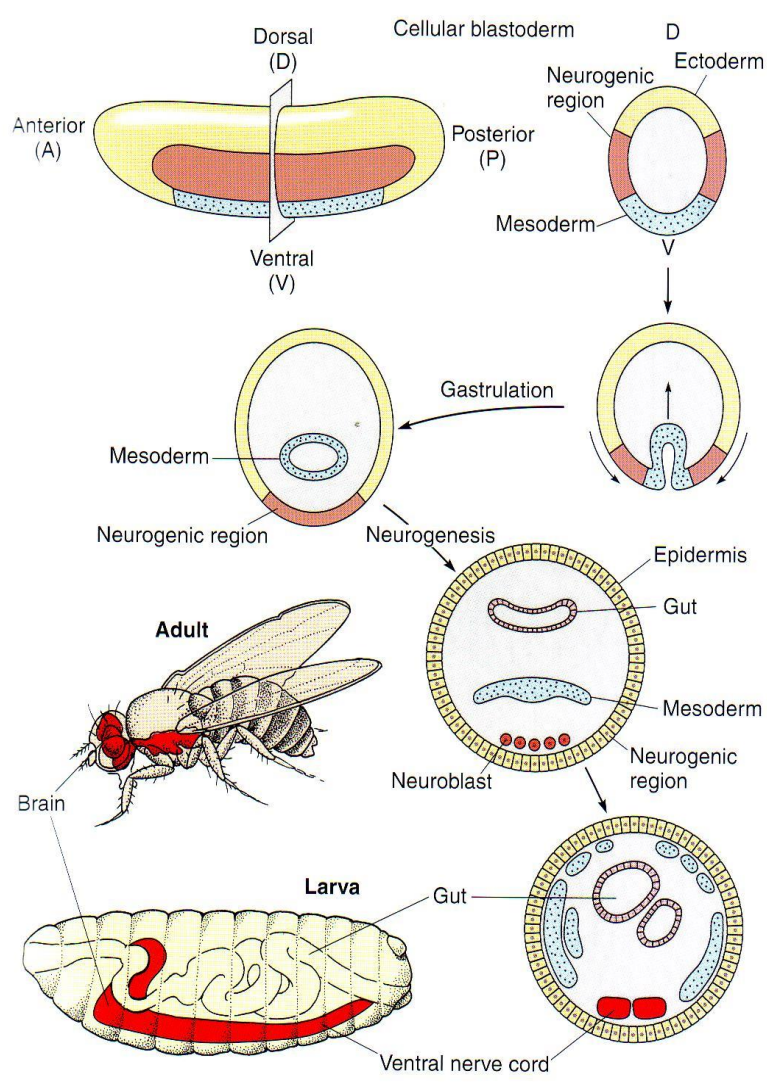
# Territori presuntivi e gastrulazione in Drosophila



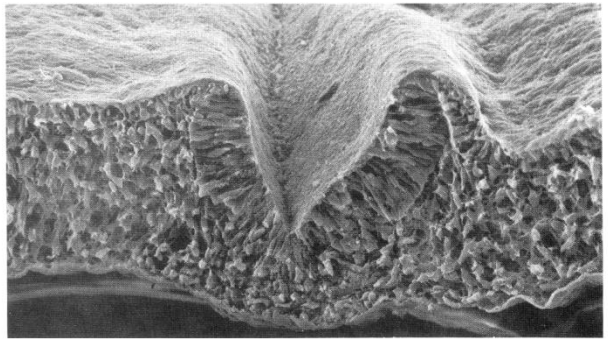



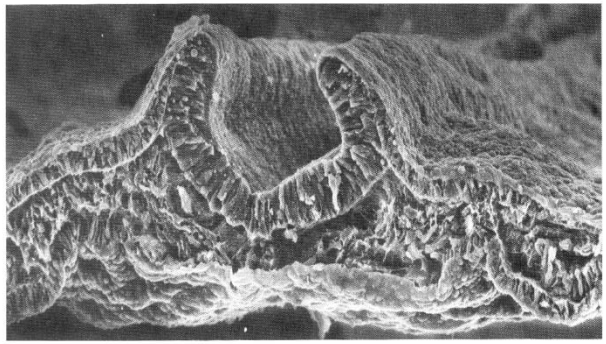
# Comparazione tra SN anfibi e artropodi

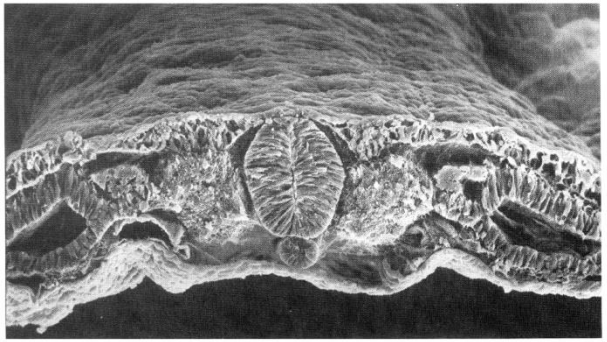


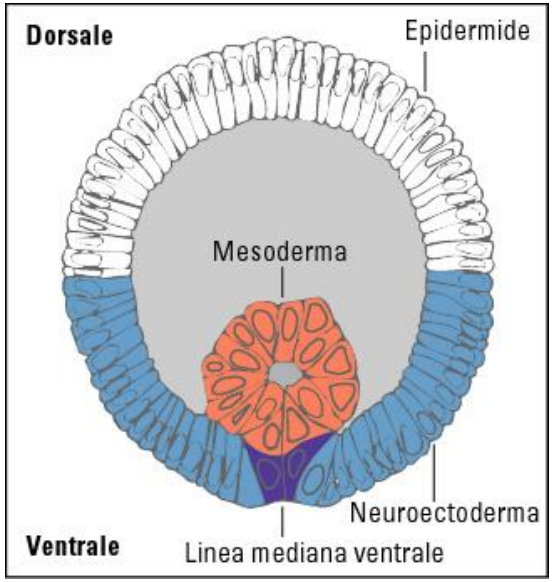
# Dorsale nei Vertebrati

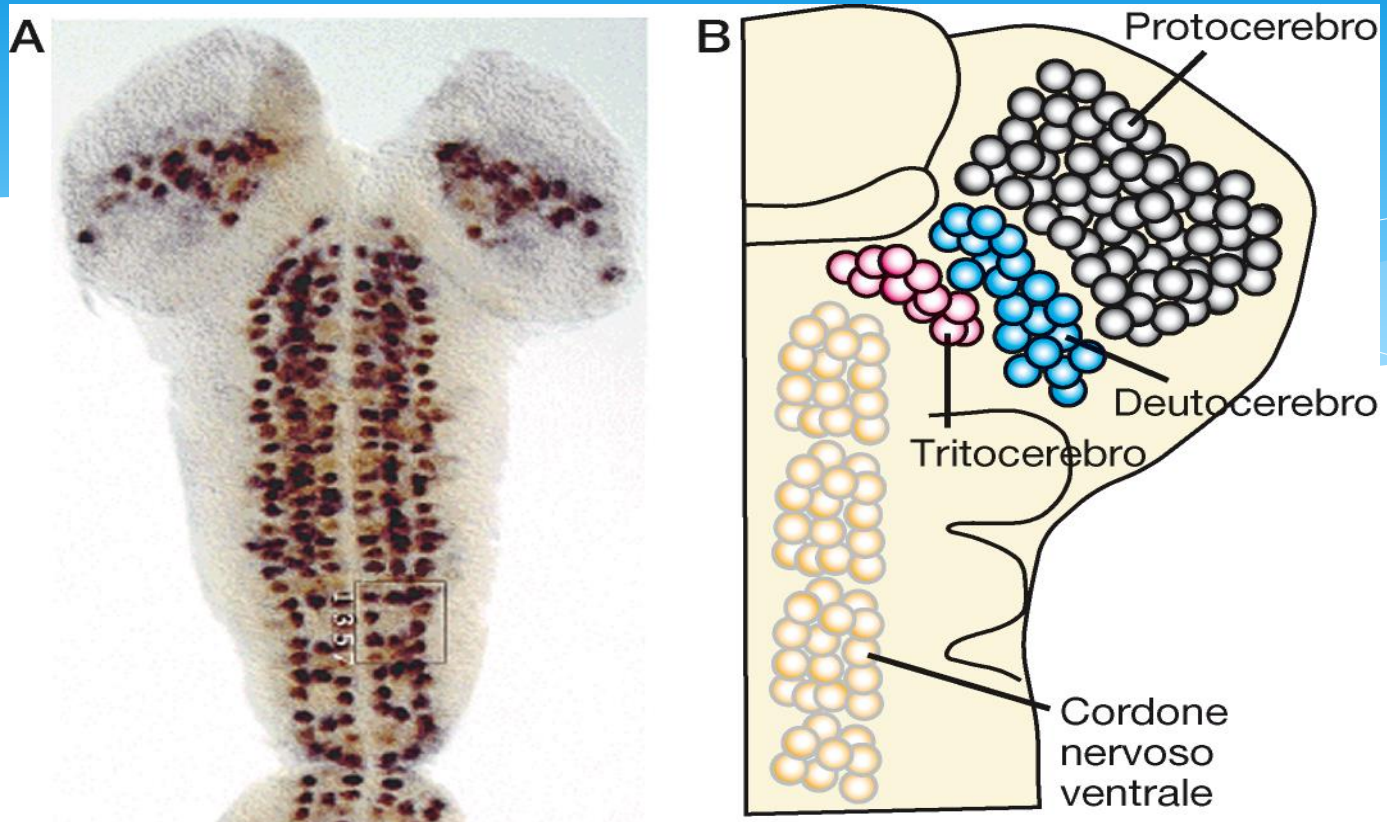






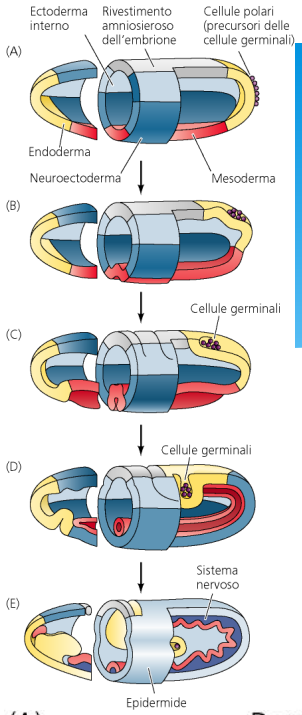
VENTRALE nell'insetto

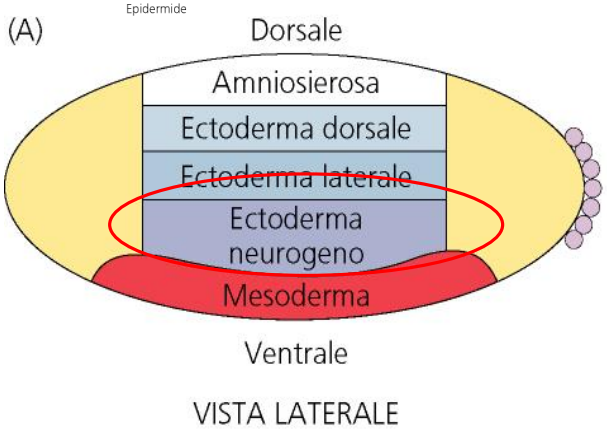


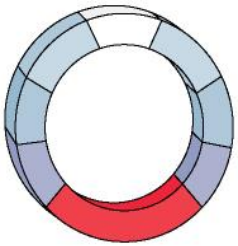



Negli invertebrati non c'è un Tubo Neurale
Ma sono presenti strutture gangliari ripetute
nei vari segmenti e nella testa

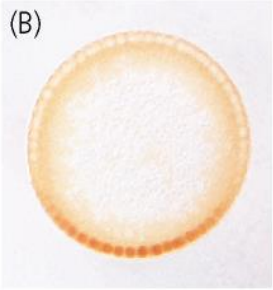
# Fattori materni guidano la specificazione dei territori ventrali



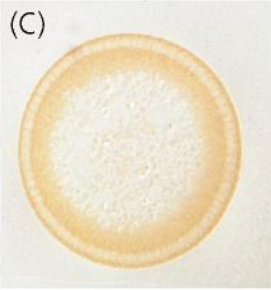



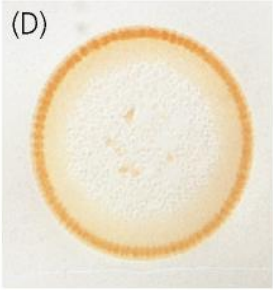

WT



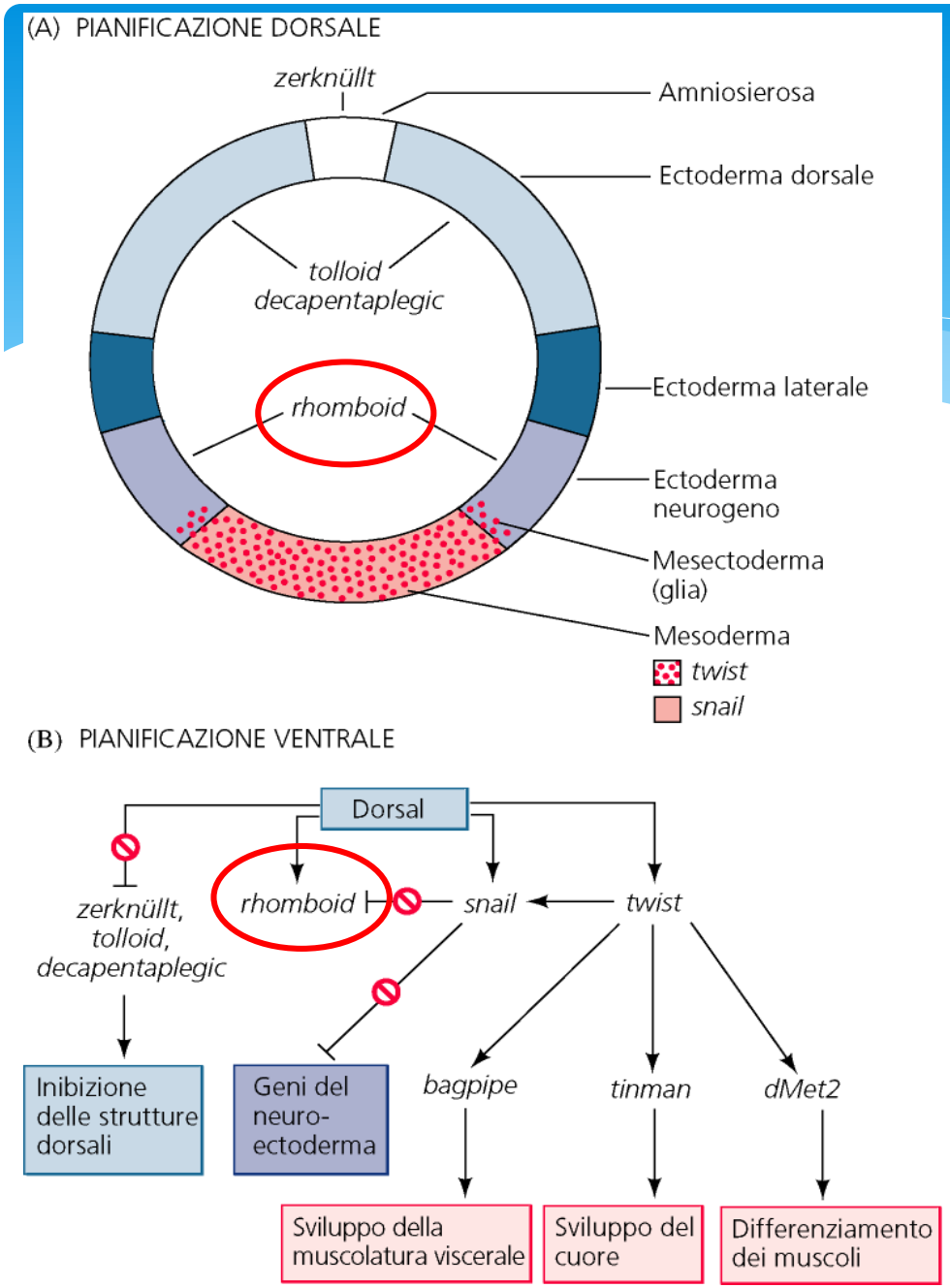

d/d -/-




Over expressione

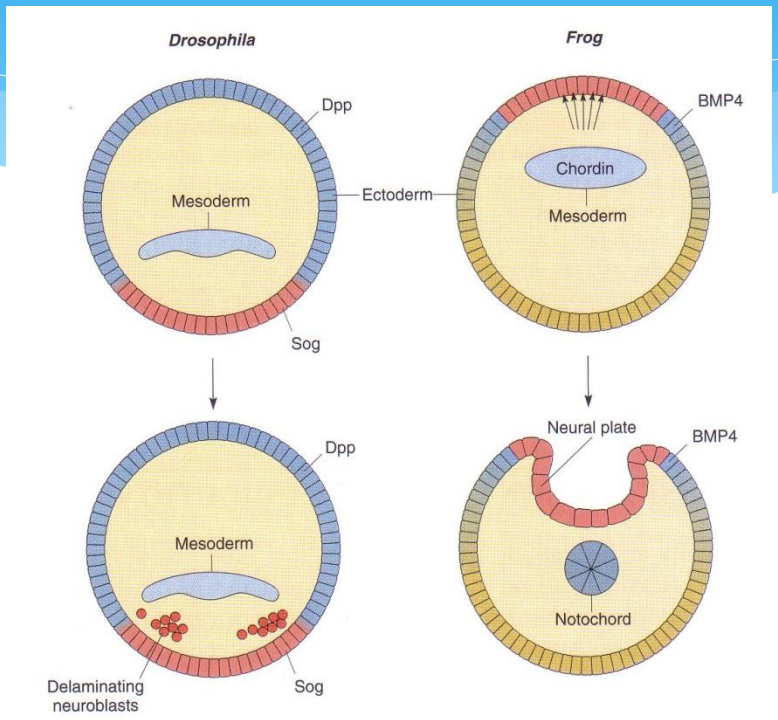



*Dorsal* è il gene ad effetto materno responsabile della definizione dell'asse dorso ventrale di Drosophila



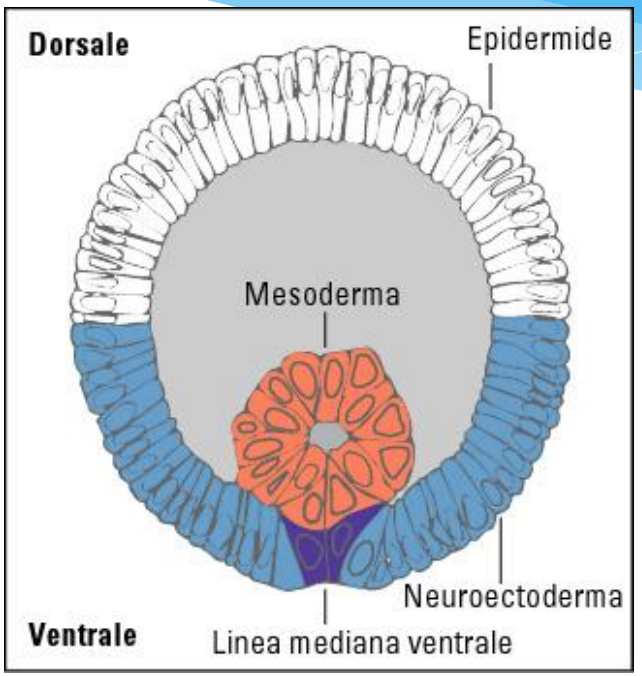

Funzioni di Dorsal

Geni ventrali ↑ Geni dorsali ↓




Sog omologo di cordina

Dpp omologo di TGFb



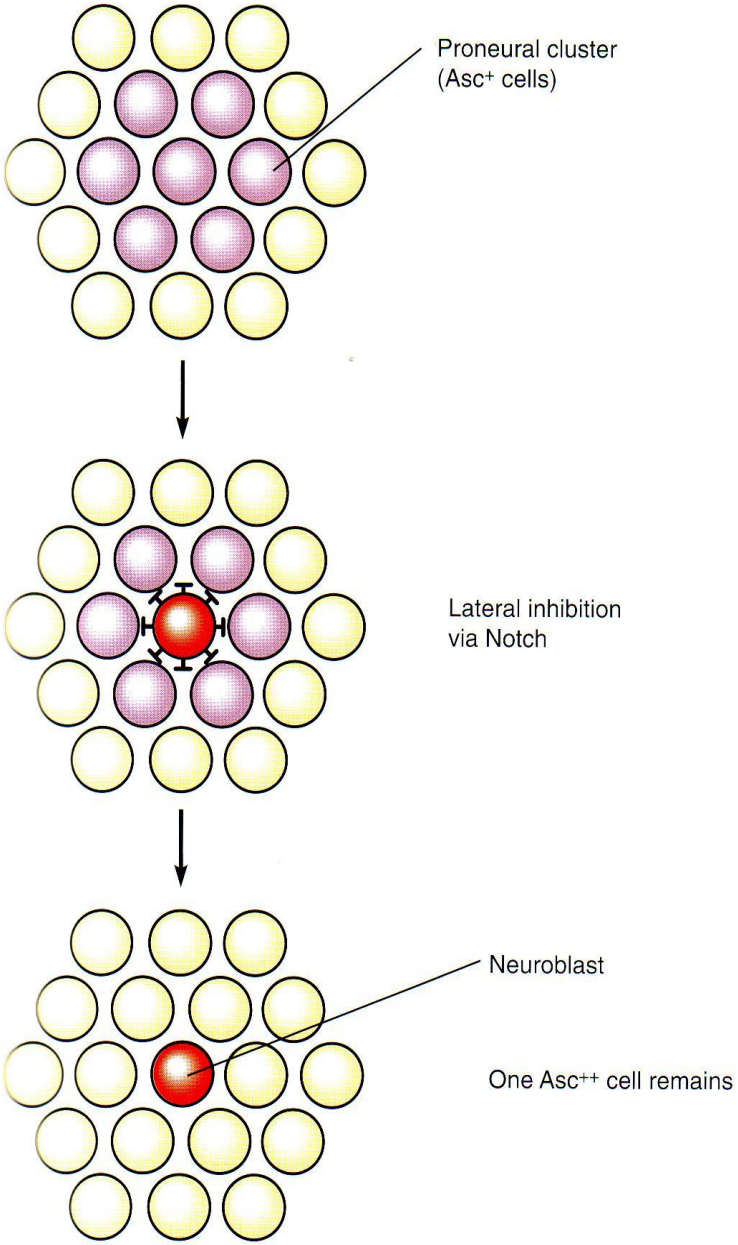

***rhomboid***

**complesso *achete-scute***

# INIBIZIONE LATERALE

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

**Accensione del sistema Delta-Notch**



# L'interazione Delta-Notch

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

NICD

CoR

CoA

NICD

MAML1

CSL- dependent

CoR

CSL

CSL

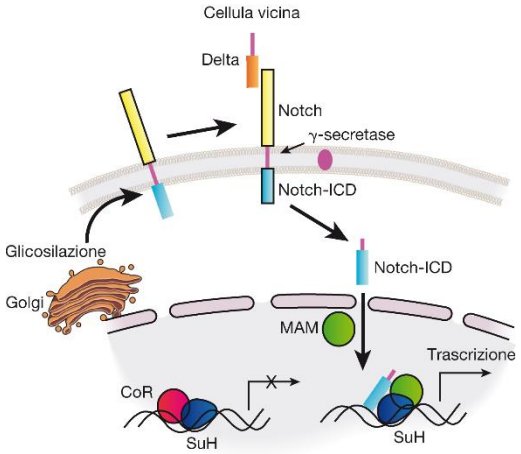
Target genes

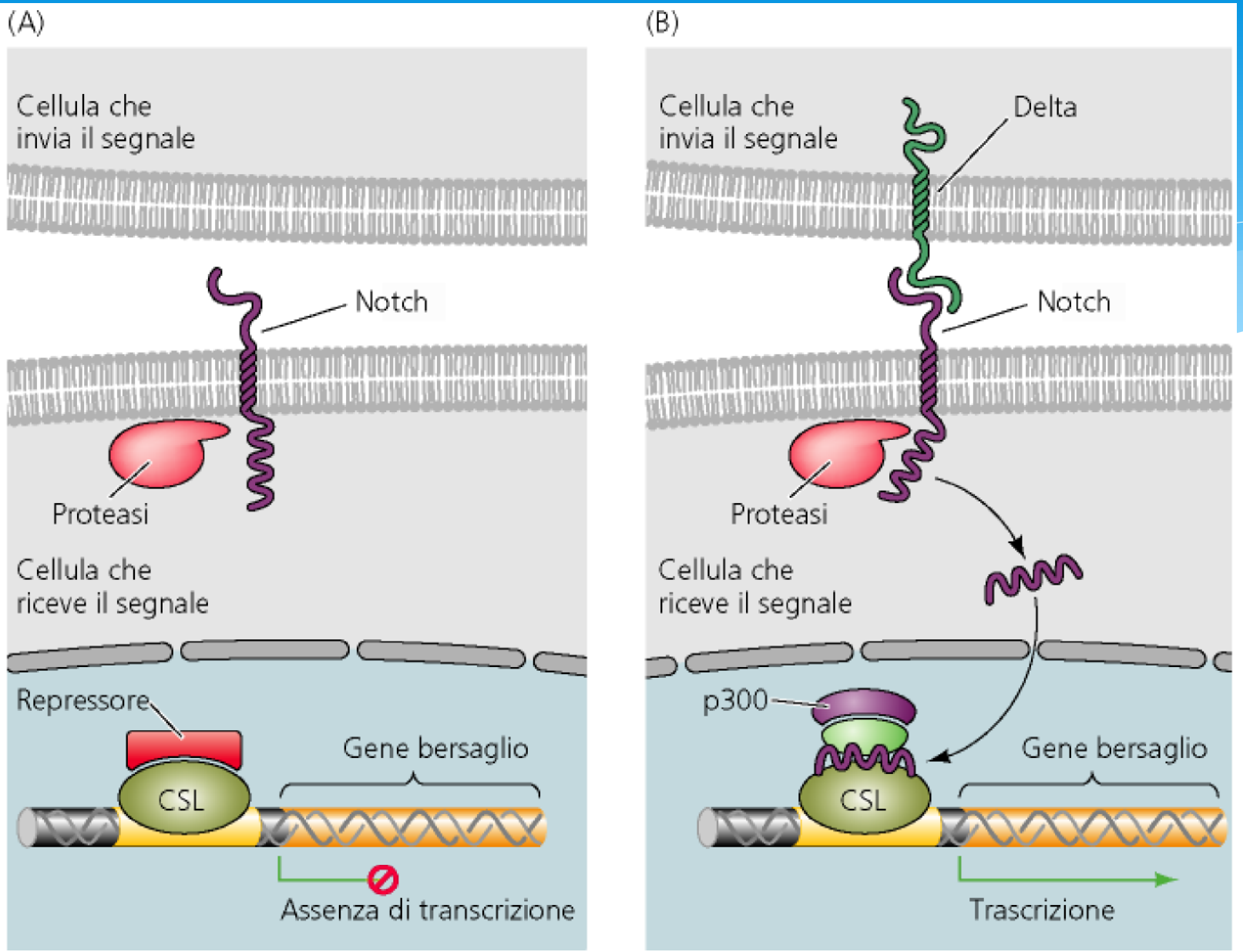
Furin-like
convertase

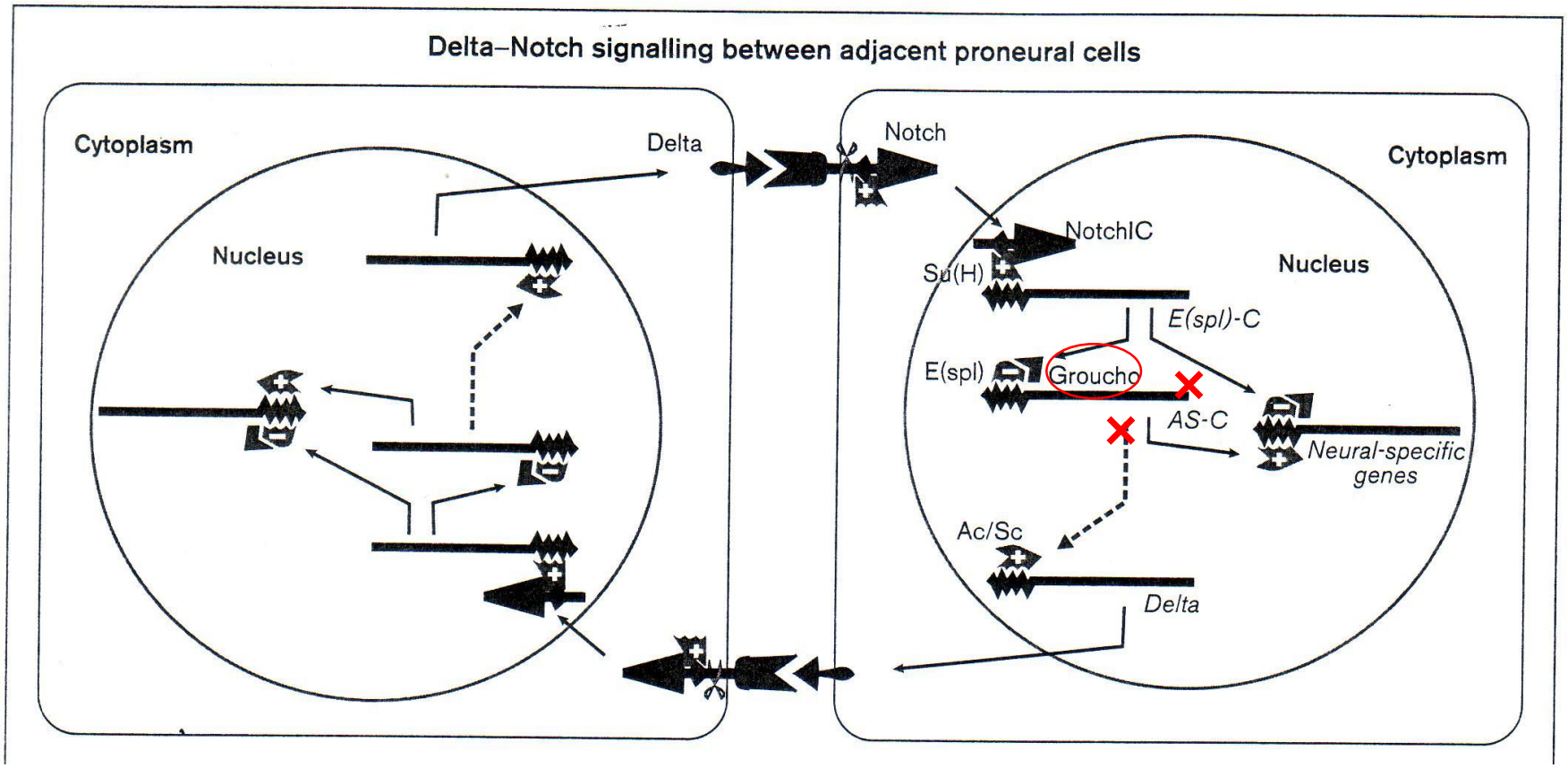
Glycolysation

Fringe

Trans-Golgi network

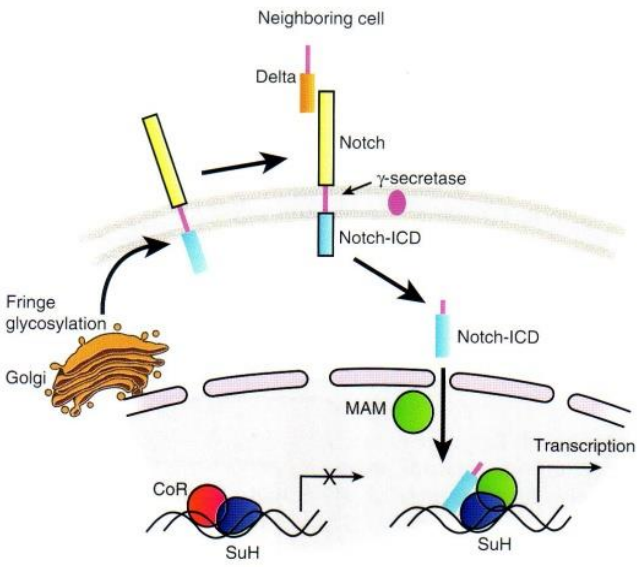



(A)
Cellula che
invia il segnale
Notch
Proteasi
Cellula che
riceve il segnale
Repressore
CSL
Gene bersaglio
Assenza di transcrizione
(B)
Cellula che
invia il segnale
Delta
Notch
Proteasi
Cellula che
riceve il segnale
p300
CSL
Gene bersaglio
Trascrizione



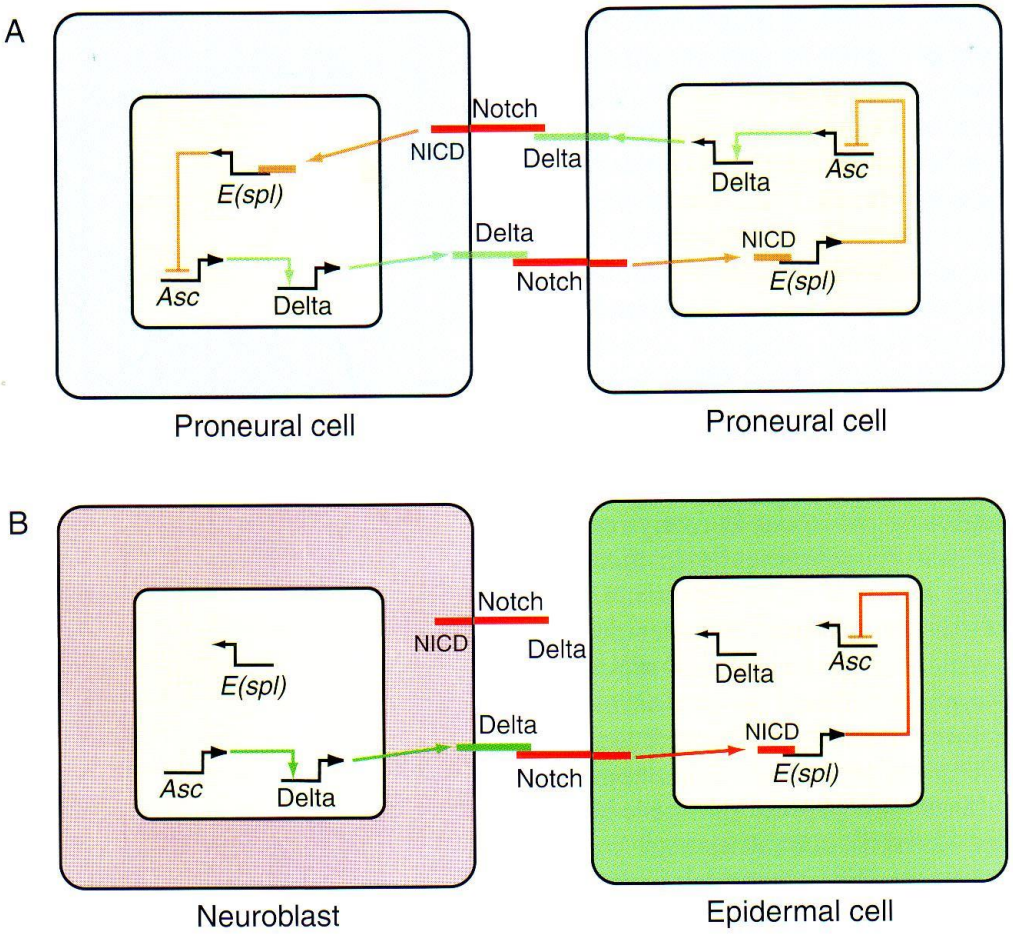

E (spl) è un fattore bHLH che è in grado di funzionare come omodimero.
Funziona da repressore genico  reclutando il co-repressore Groucho

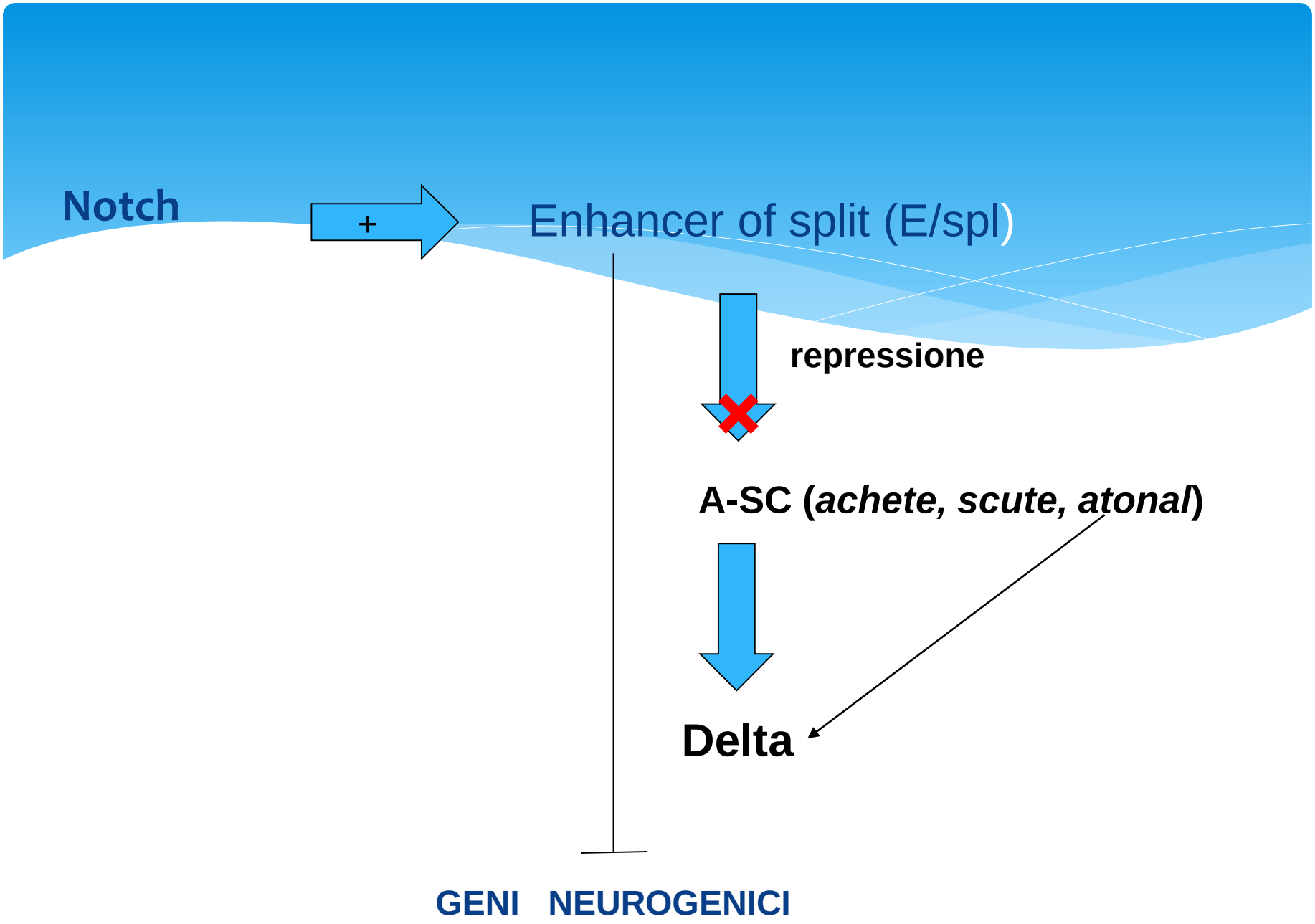
# Meccanismo di inibizione laterale



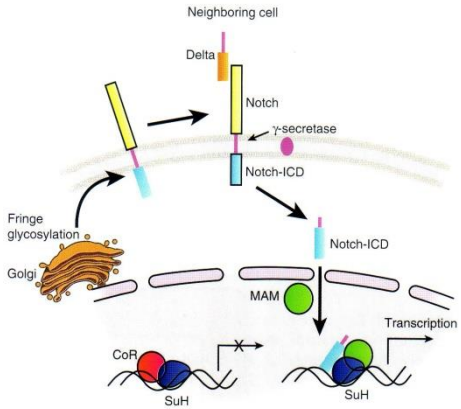

Notch → E(spl)

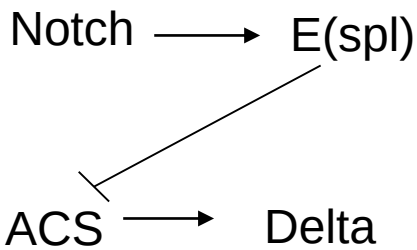
ACS → Delta

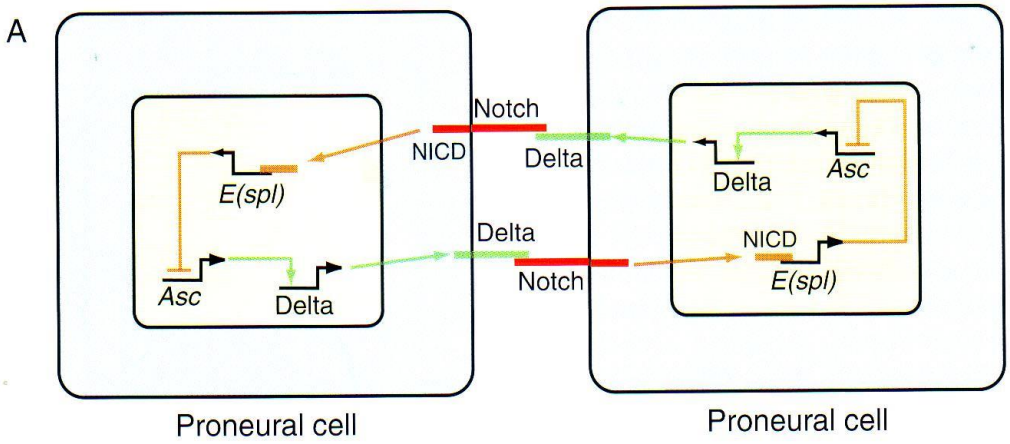


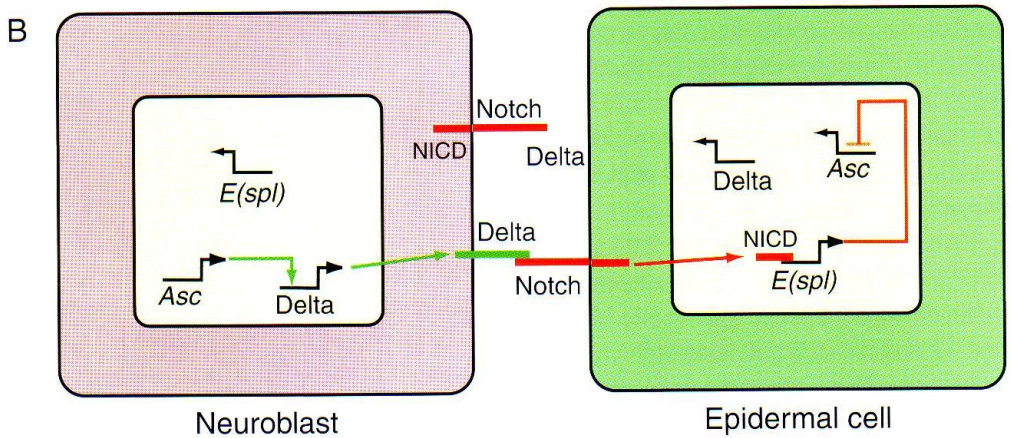

Notch
+
Enhancer of split (E/spl)
repressione
A-SC (*achete, scute, atonal*)
Delta
GENI NEUROGENICI

# Meccanismo di inibizione laterale

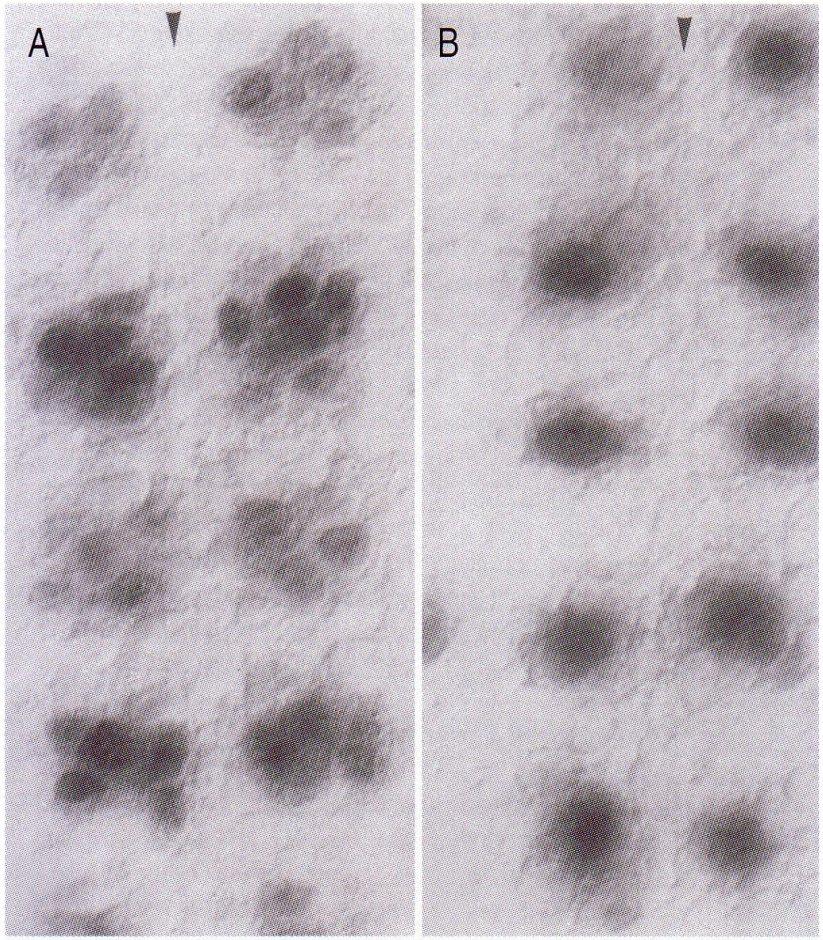


Clusters pro-neurali Neuroblasti



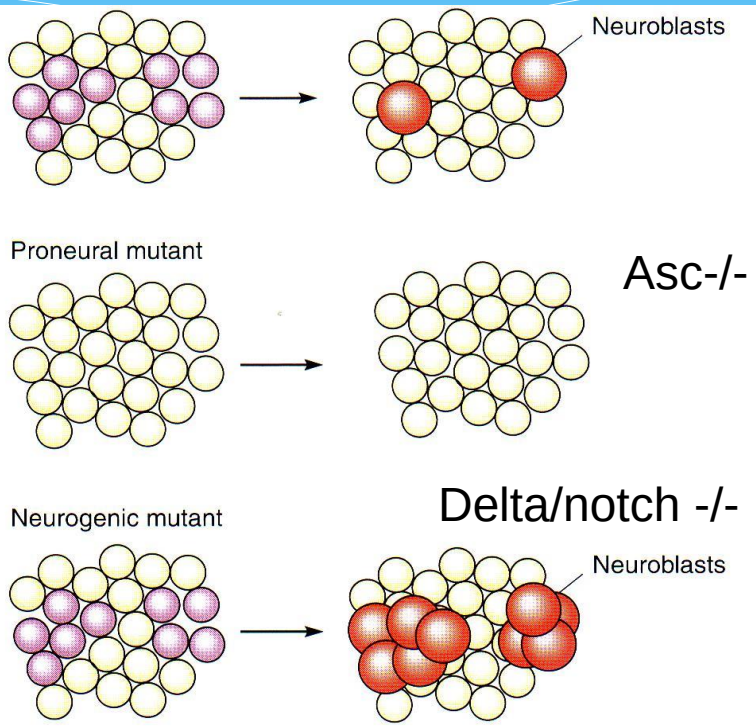
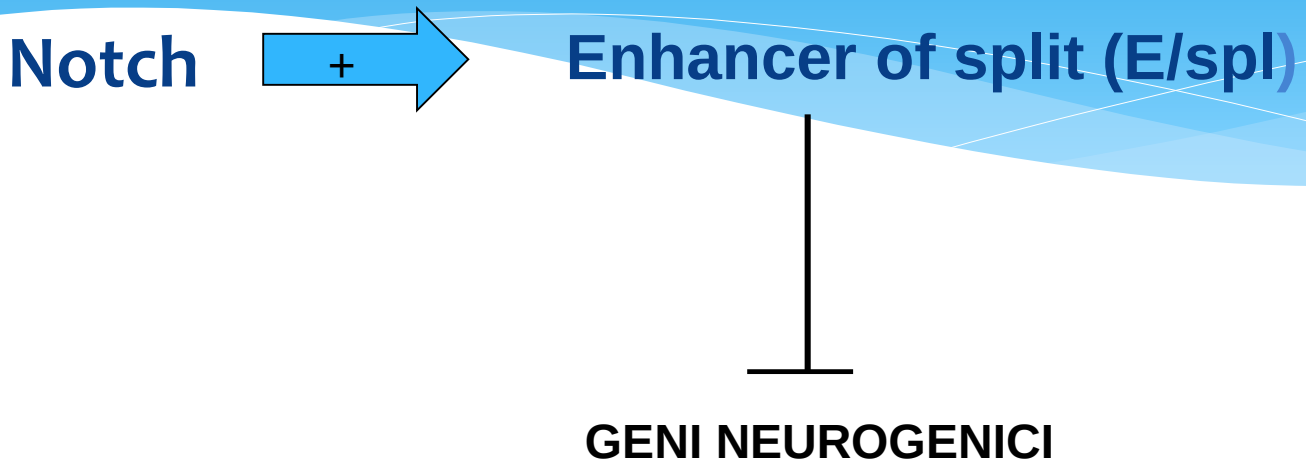




**Fig. 1.24** Neurogenic genes and proneural genes were first identified in the *Drosophila* due to their effects on neural development. In the wild type


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

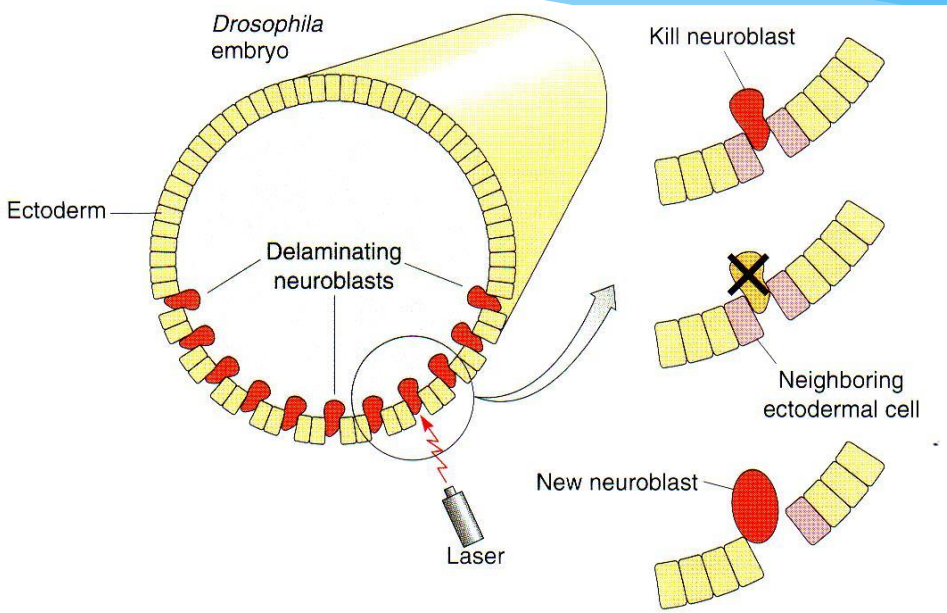
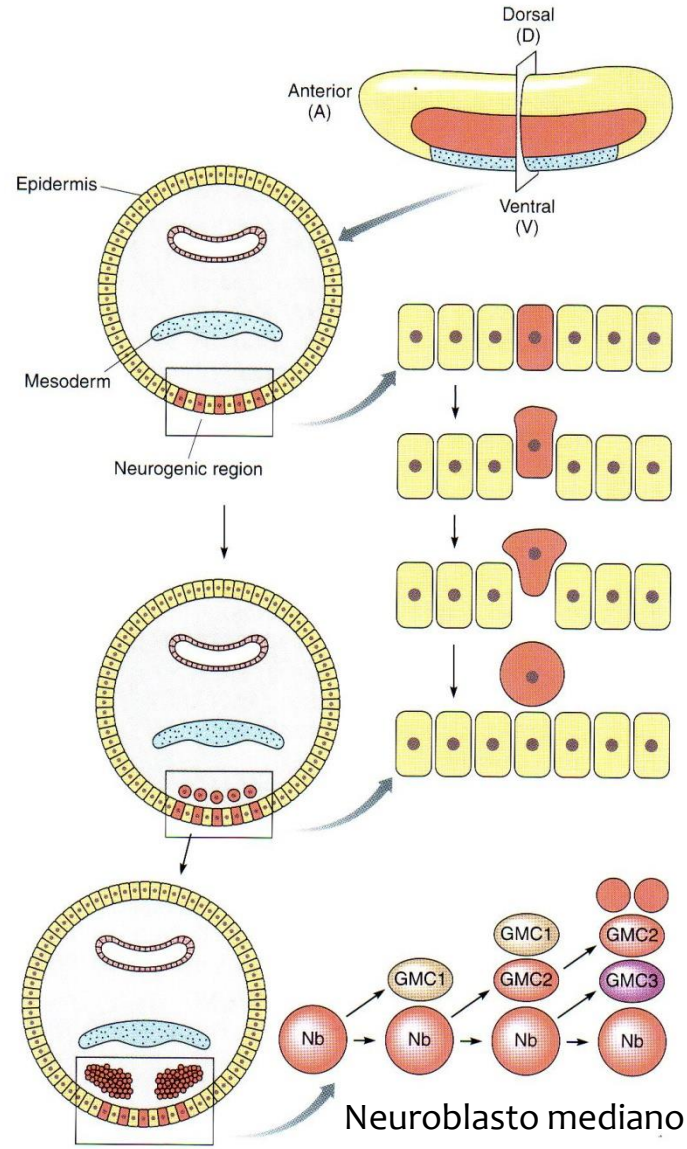


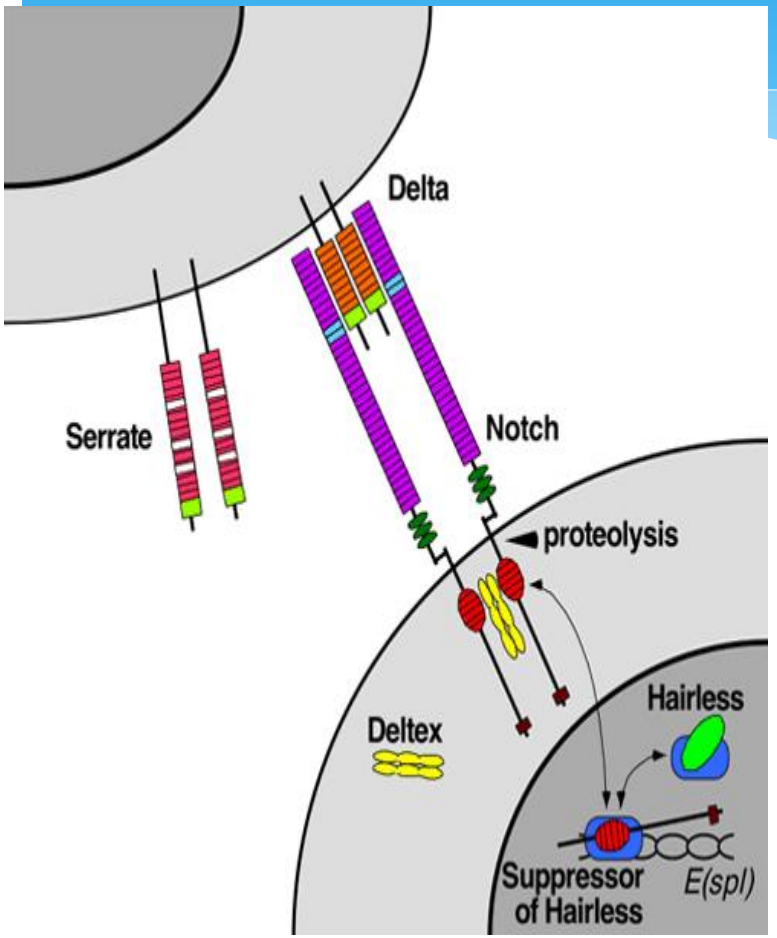

**Fig. 1.26** Ablation of the delaminating neuroblast with a laser microbeam directed to the ventral neurogenic region of the fly embryo causes a neighbor-



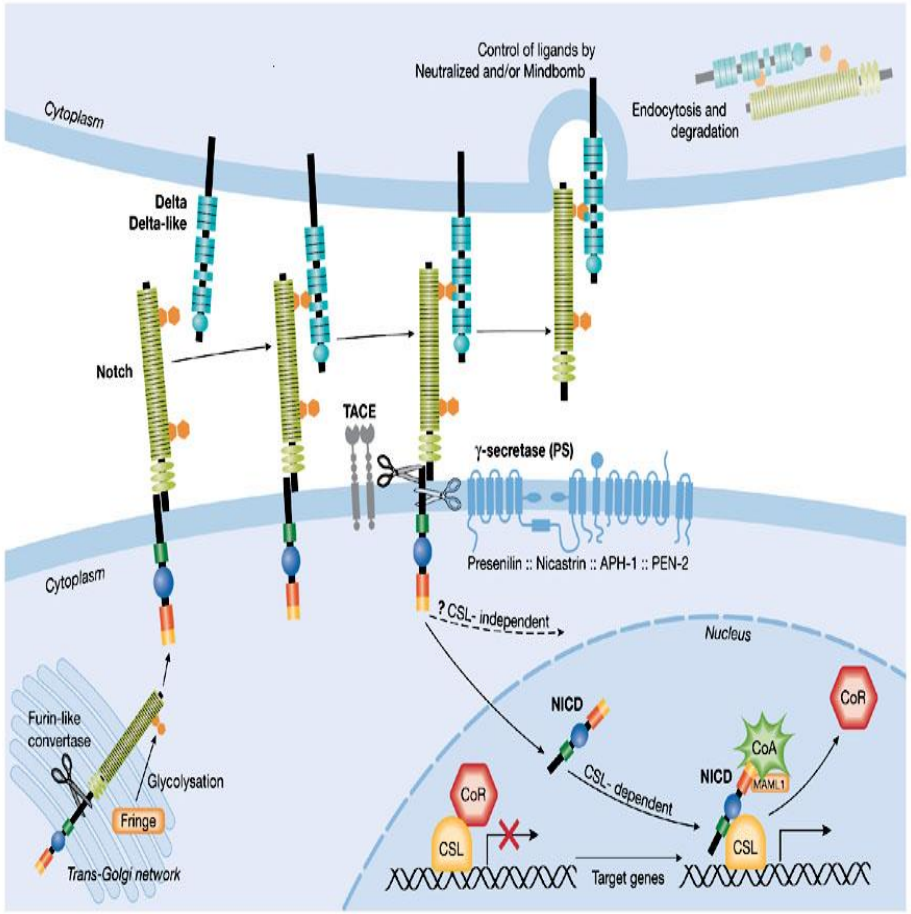
L’interferenza delle via TgfB è comune in anfibio e insetto

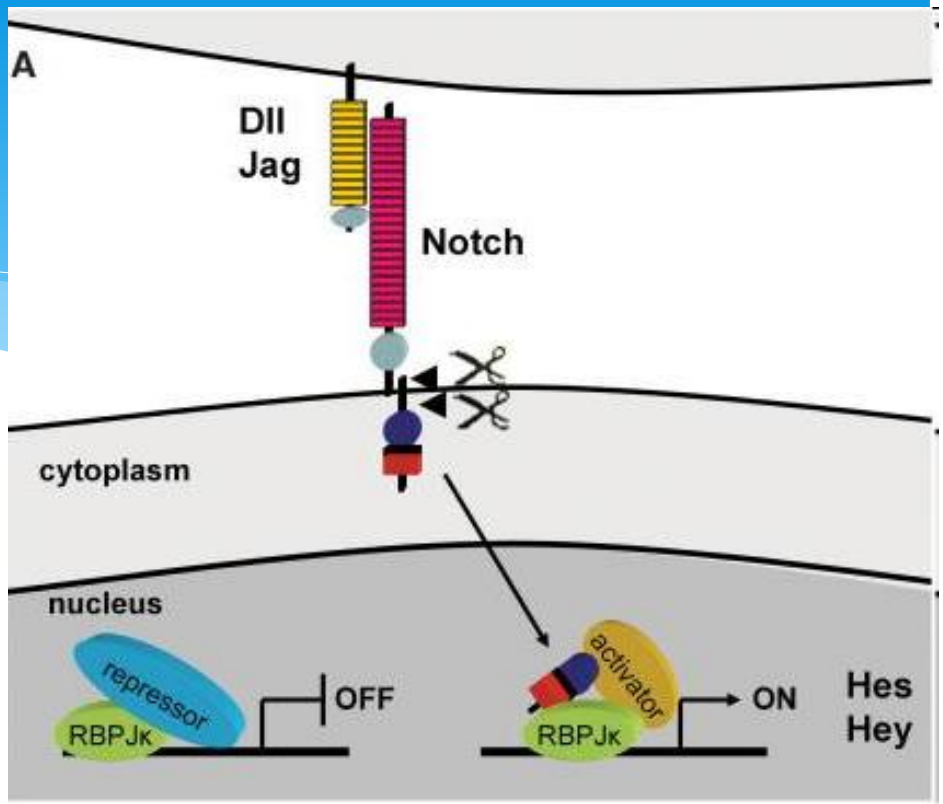
Il sistema Delta-Notch è presente nel vertebrato????

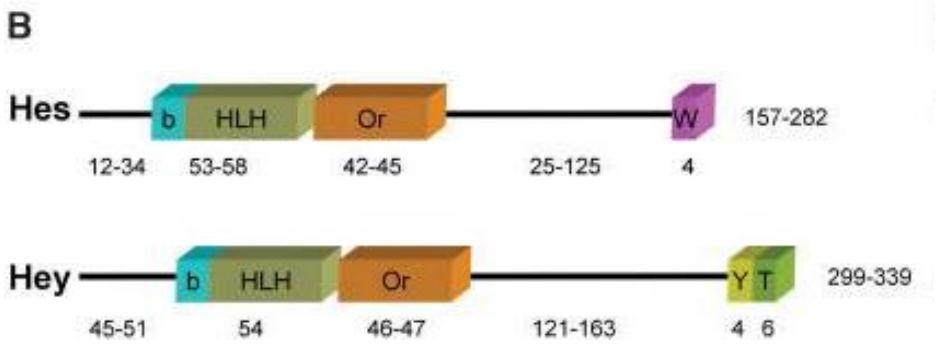
# Ligandi di Notch




1. Delta
2. Serrate
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
NICD
CoR
CoA
MAML1
NICD
CSL- dependent
CoR
CSL
CSL
Target genes
Furin-like
convertase
Glycolysation
Fringe
Trans-Golgi network


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)

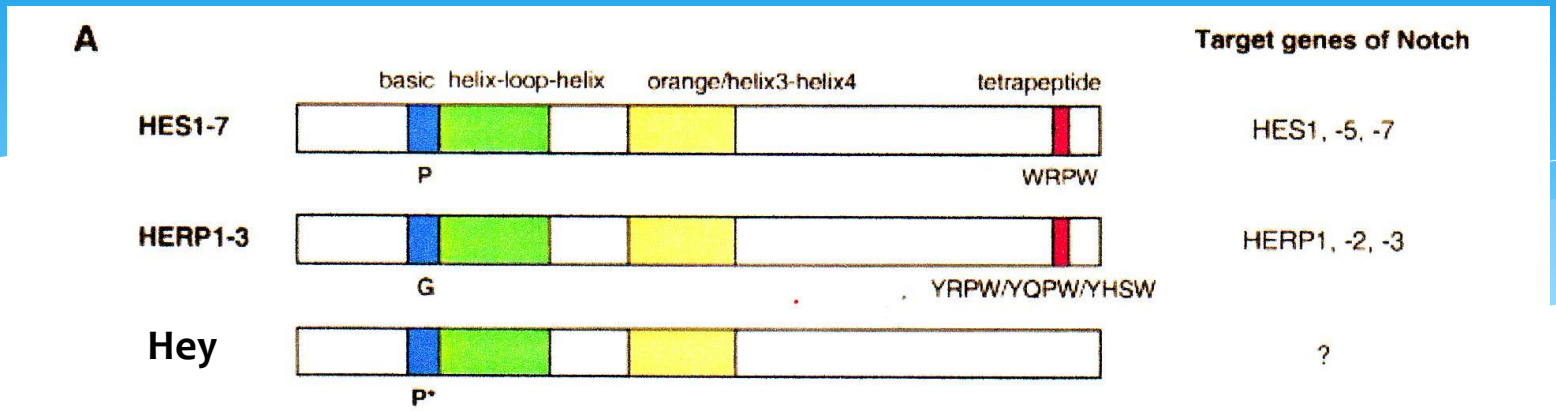
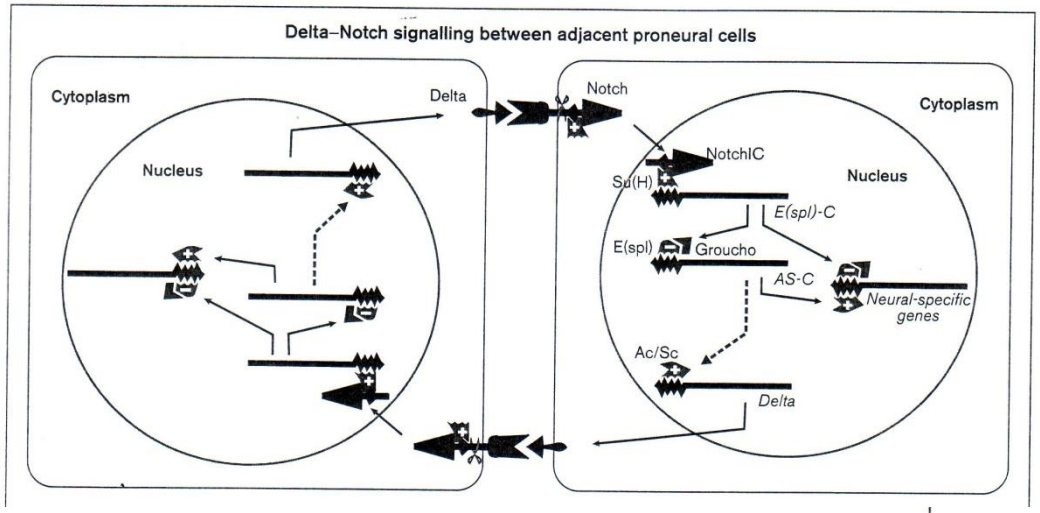


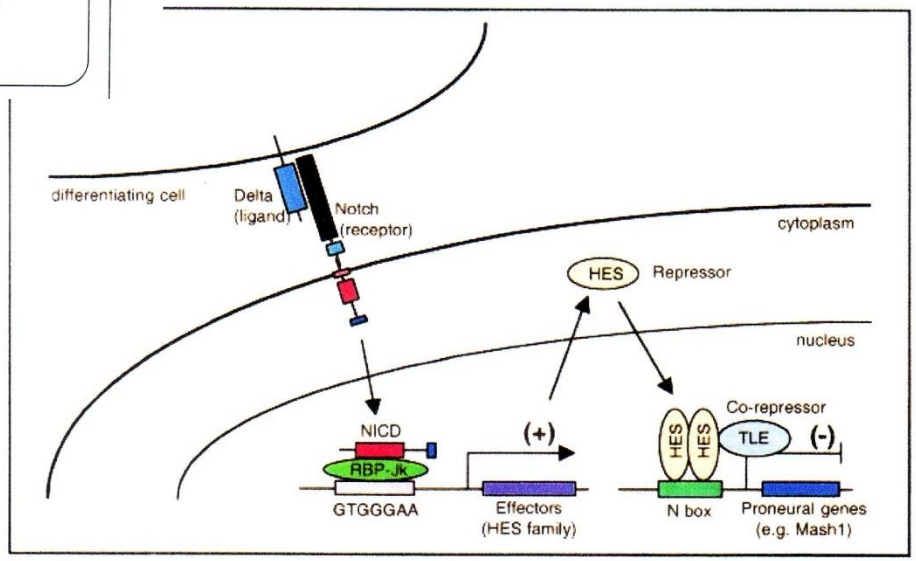

TABLE 2B. Consensus binding site HLH transcription factors

| 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.

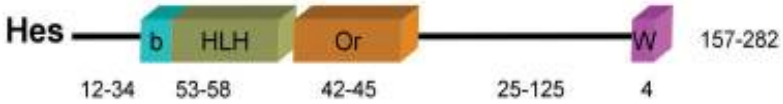
HLH di classe C (repressori trascrizionali) Comprende geni HES, HERP e Hey




## Meccanismi di repressione genica

HLH funzionano come dimeri

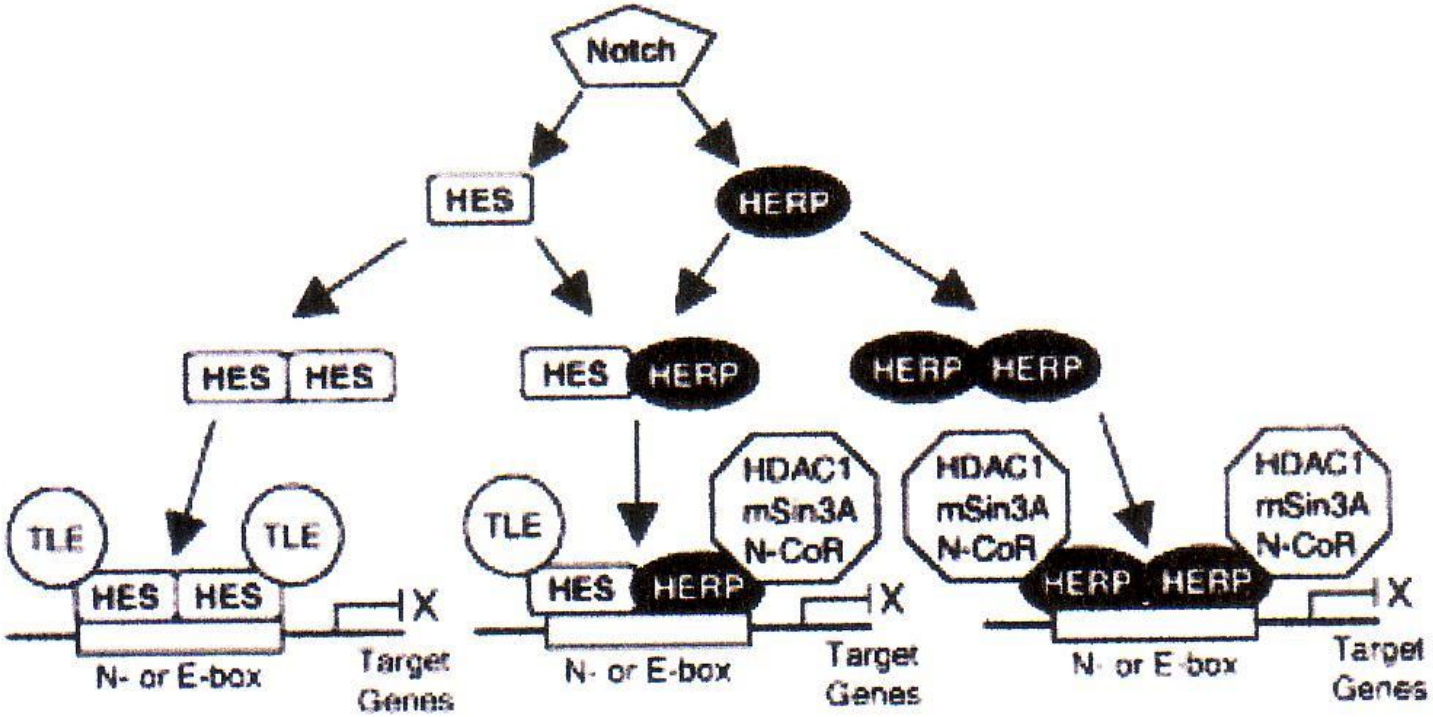



1. Hes può omodimerizzare

**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)