# Signaling Pathways in Developmental Processes

# Embryo development & signaling pathways

Developmental processes of a multicellular organism involve **different cellular behaviors** (e.g., proliferation, migration, differentiation): their regulation must be tightly controlled in **space** and **time**.

A limited number of **key signaling pathways** coordinate the different cell behaviors leading to organogenesis.

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?

**How the same signals can elicit different cellular responses?**

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→The specific **competence of the receiving cells** plays a central role in the interpretation of signaling molecules.

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A limited number of **key signaling pathways** coordinate the different cell behaviors leading to organogenesis.

→The specific **competence of the receiving cells** plays a central role in the interpretation of signaling molecules.

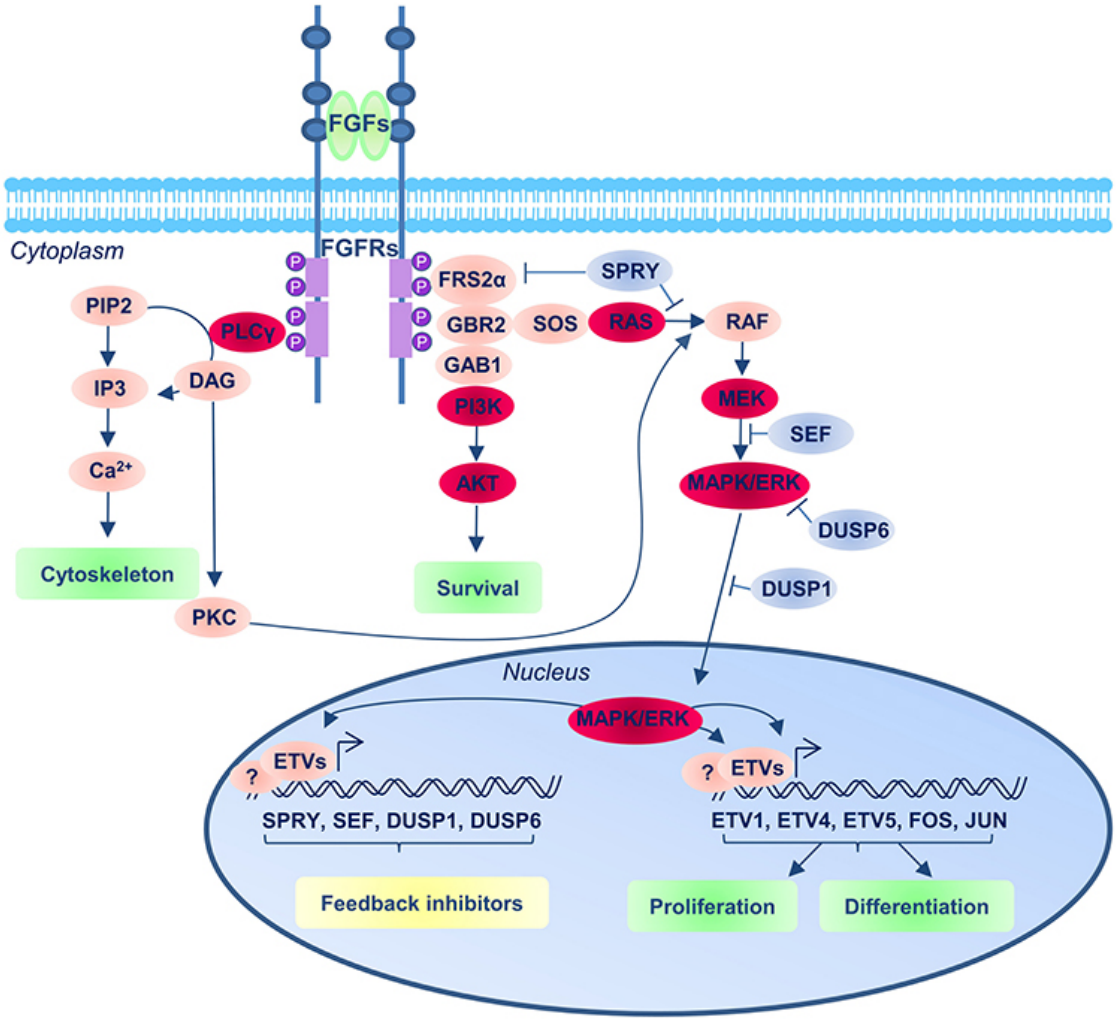
→Key signaling pathways **are highly conserved during evolution**.

# Embryo development & signaling pathways

Relevant signaling pathways for neural development include:

- Fibroblast Growth Factor – **FGF**
- Wingless proteins family - **WNT**
- Sonic Hedgehog **SHH**
- Bone Morphogenetic Protein – **BMP**
- Retinoic Acid - **RA**
- **NOTCH**

# FGF Signaling




Diez del Corral and Morales, Front. Cell Dev. Biol.(2017)

Fibroblast growth factors (FGFs)
bind to FGF receptors (FGFRs)

↓

Receptor dimerization
TK Activation
transphosphorylation
of FGFRs intracellular domain

↓

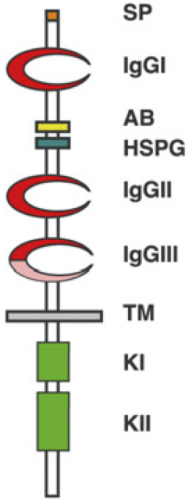
Recruitment of adapter molecules
and second messengers

↓

Downstream cascades activation

# FGF Signaling

Up to 23 Fgf genes - 4 FGFRs in vertebrates

| LIGANDS | | | | RECEPTORS | | |
|---|---|---|---|---|---|---|
| Scheme | Family | | Members | FGFR | Isoforms | Scheme |
|   | *cFGFs* | FGF4 | FGF3 | *1, 2* | IIIb |   |
| | | | FGF4 | 1, 2, *3*, 4 | IIIc | |
| | | | FGF6 | *1, 2,* 4 | | |
| | | FGF5 | FGF1 | 1, 2, 3, 4 | IIIb, IIIc | |
| | | | FGF2 | 1, 2, 3, 4 | | |
| | | | FGF5 | *1, 2* | IIIc | |
| | | FGF8 | FGF8 | *1*, 2, **3, 4** | IIIc | |
| | | | FGF17 | *1*, 2, 3, *4* | | |
| | | | FGF18 | *2, 3, 4* | | |
| | | FGF9 | FGF9 | *2*, 3 | IIIb, IIIc | |
| | | | FGF16 | *2, 3* | IIIc | |
| | | | FGF20 | *1, 2,* 3, *4* | IIIb, IIIc | |
| | | FGF10 | FGF7 | **2, 4** | IIIb | |
| | | | FGF10 | *1, 2* | | |
| | | | FGF22 | *1, 2* | | |
| | *hFGFs* | FGF15/19 | FGF15/19 | 1, **2, 3, 4** | IIIb, IIIc | |
| | | | FGF21 | *1*, 2, *3*, **4** | | |
| | | | FGF23 | *1*, 2, *3*, **4** | | |
| | *iFGFs* | FGF11 | FGF11 | | | |
| | | | FGF12 | | | |
| | | | FGF13 | | | |
| | | | FGF14 | | | |

Guillemot and Zimmer, Neuron 2011

# FGF Signaling

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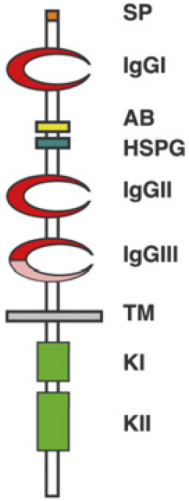
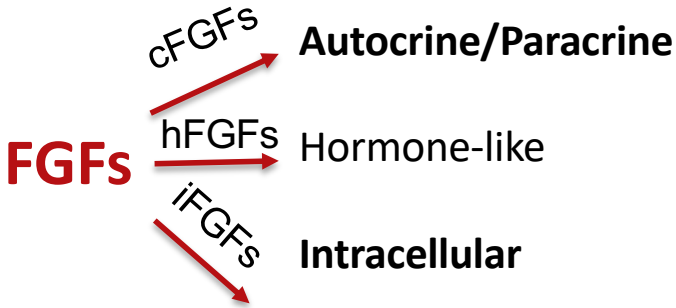
|   | cFGFs: FGF4 | FGF3 | *1, 2* | IIIb |   |
| | | FGF4 | 1, 2, *3*, 4 | IIIc | |
| | | FGF6 | *1, 2,* 4 | | |
| | FGF5 | FGF1 | 1, 2, 3, 4 | IIIb, IIIc | |
| | | FGF2 | 1, 2, 3, 4 | | |
| | | FGF5 | *1, 2* | IIIc | |
| | FGF8 | FGF8 | *1*, 2, **3, 4** | IIIc | |
| | | FGF17 | *1*, 2, 3, *4* | | |
| | | FGF18 | *2, 3, 4* | | |
| | FGF9 | FGF9 | *2*, 3 | IIIb, IIIc | |
| | | FGF16 | *2, 3* | IIIc | |
| | | FGF20 | *1, 2,* 3, *4* | IIIb, IIIc | |
| | FGF10 | FGF7 | **2, 4** | IIIb | |
| | | FGF10 | *1, 2* | | |
| | | FGF22 | *1, 2* | | |
| | hFGFs: FGF15/19 | FGF15/19 | 1, **2, 3, 4** | IIIb, IIIc | |
| | | FGF21 | *1*, 2, *3*, **4** | | |
| | | FGF23 | *1*, 2, *3*, **4** | | |
| | iFGFs: FGF11 | FGF11 | | | |
| | | FGF12 | | | |
| | | FGF13 | | | |
| | | FGF14 | | | |

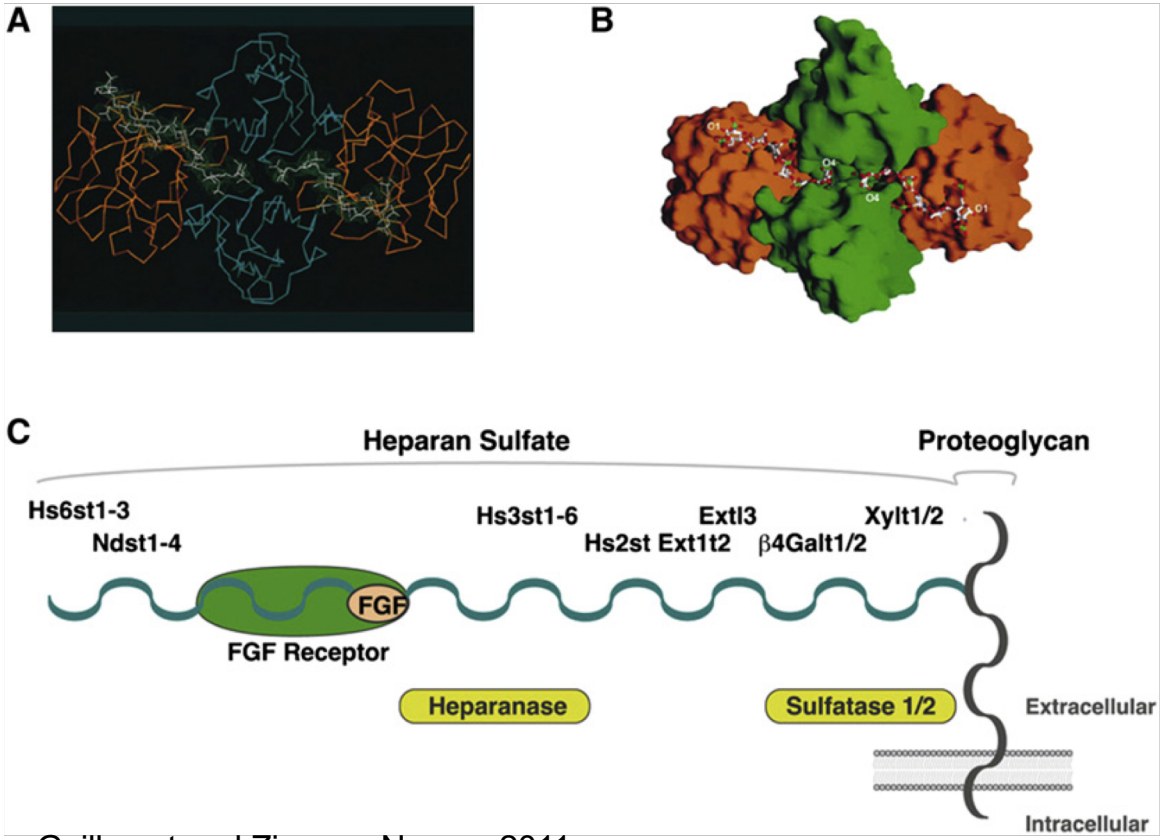



Guillemot and Zimmer, Neuron 2011

# FGF Signaling regulatory mechanisms : HSPGs

HSPGs are required for:

- high affinity and specificity in binding of FGF-FGFR;
- bridging of FGFR dimers for autophosphorylation;
- limit FGF diffusion
- Protect FGF from degradation




Guillemot and Zimmer, Neuron 2011

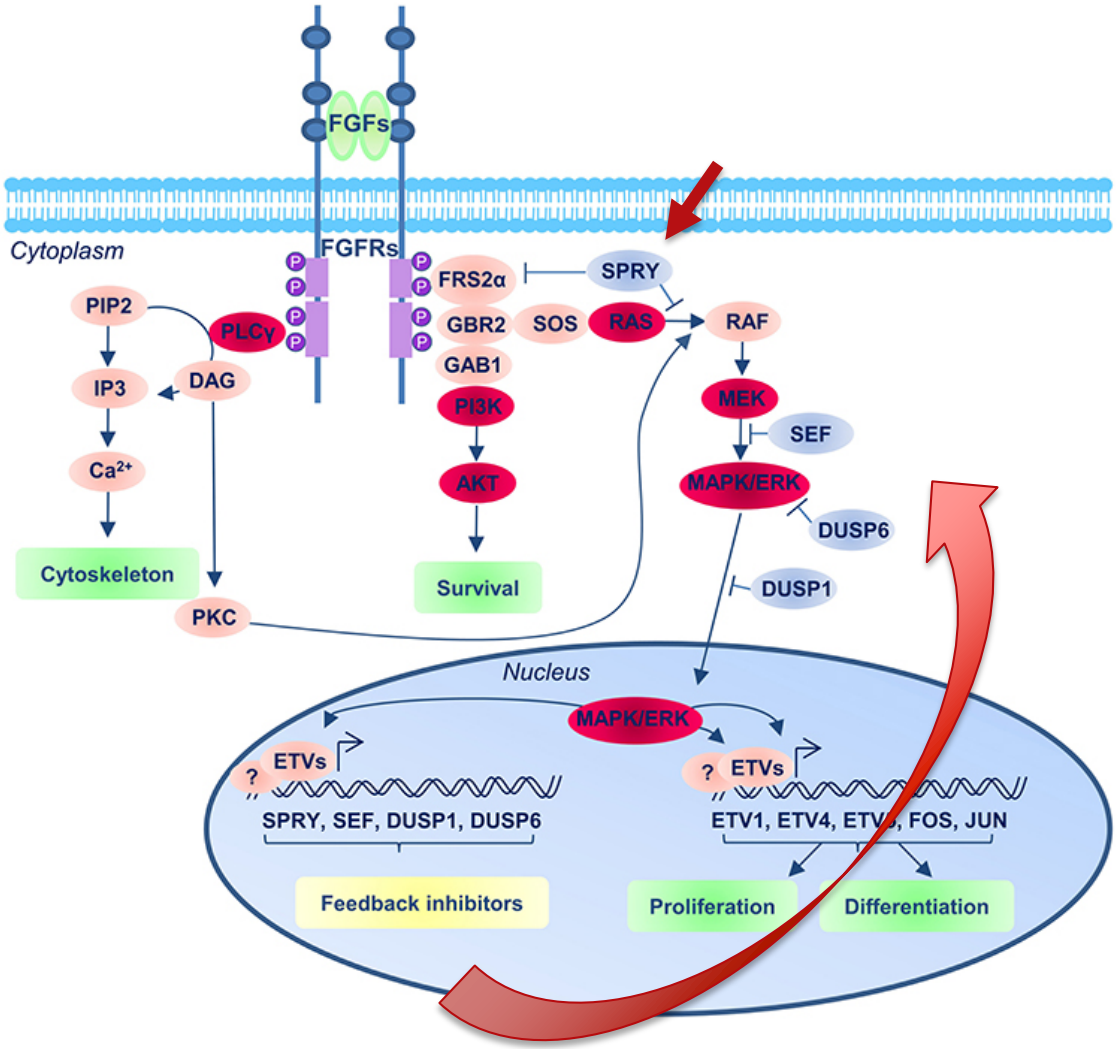
Ternary Complexes Comprising FGFs, FGFRs, and Heparan Sulfate Proteoglycans

FGF2 (orange), FGFR1 (blue), and the heparan sulfate moiety of a heparan sulfate Proteoglycan (HSPG) (white).

Regulation of HSPG synthesis can modulate FGF signaling extensively.
Twenty-six enzymes are responsible for the assembly of heparan sulfate chains.

Enzymes that cleave
heparan sulfate chains (heparanases) or remove the sulfates (sulfatases) have also been shown to modulate FGF signaling.

# FGF Signaling regulatory mechanisms: feedback loops




Diez del Corral and Morales, Front. Cell Dev. Biol.(2017)

**Neural induction**

Acquisition of neural fate
Amphibia – fish - birds

# The Multiple roles of FGF in neural development

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**Neural induction**

**Neural patterning**

Positional information: specification of posterior neural fates

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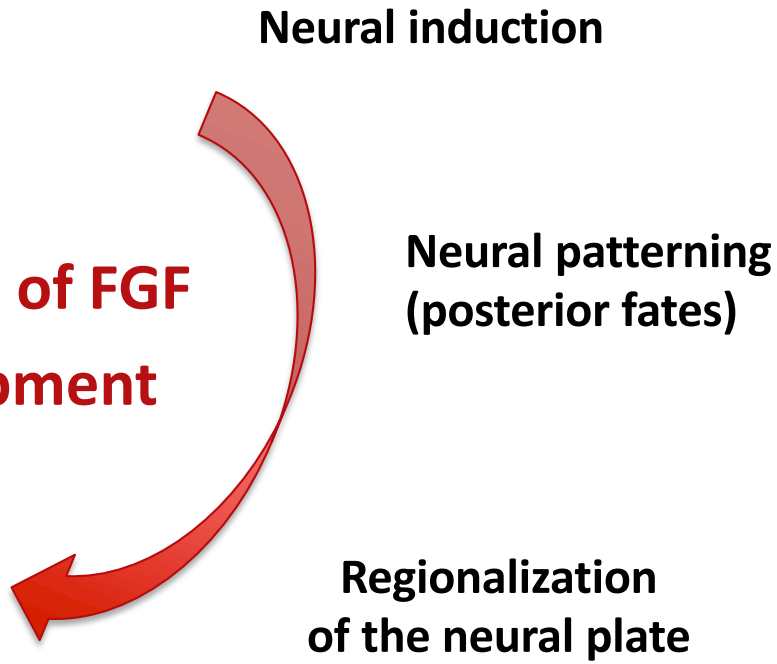
**Neural induction**

**Neural patterning**

Positional information: specification of posterior neural fates

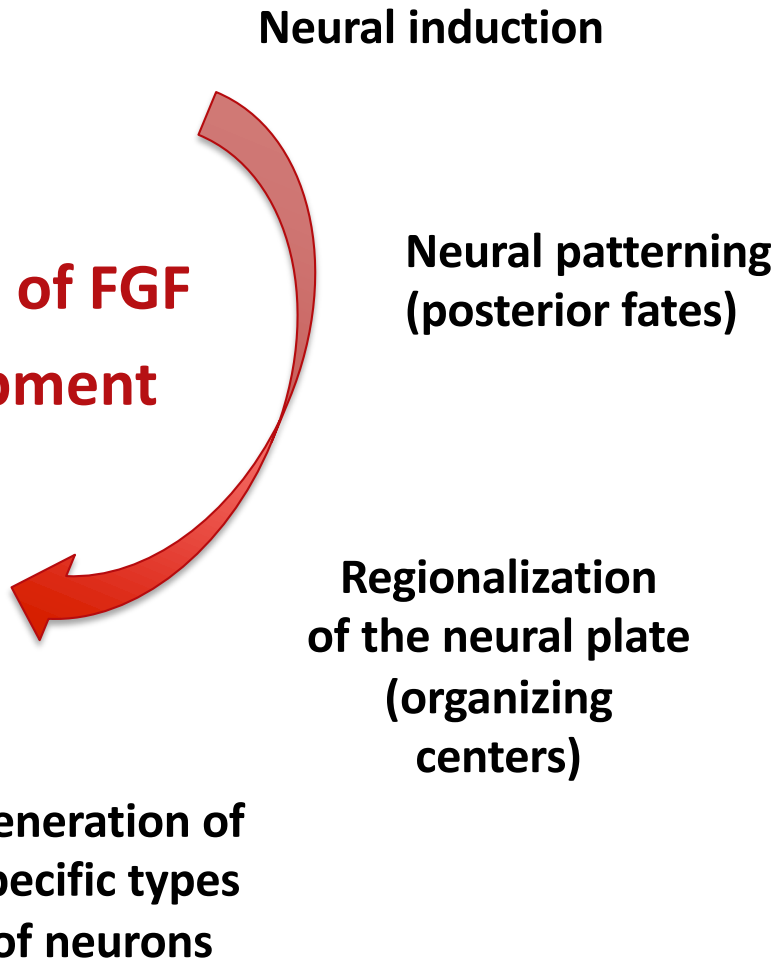
<u>PNS</u>
Neural crest
Ectodermal placodes
(e.g. FGF3 & FGF8 otic plac.
FGF8 olfactory placode)

## The Multiple roles of FGF in neural development




Local organizing centers (e.g rostral signaling center; isthmic organizer)
Sequential involvement of FGFs in region specification
and in specific cell type generation

# The Multiple roles of FGF in neural development




(e.g. FGF8 Cajal-Retzius neurons – GnRH neurons)

# The Multiple roles of FGF in neural development

**Neural induction**

**Neural patterning (posterior fates)**

**Regionalization of the neural plate (organizing centers)**

**Generation of specific types of neurons**

**Differential growth of cortical subdomain**

**Specification of cortical areal identities**

(e.g. FGF8 patterns the anterior cortex)

## At a cellular level

**Proliferation**

e.g. Neuroepithelial cells
(FGF2 and FGF8)

**Neural induction**

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## At a cellular level

**Gliogenesis**

**Proliferation**

e.g. switch from neurogenesis to gliogenesis in the cortex (FGF2 )

# The Multiple roles of FGF in neural development

**Neural induction**

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## At a cellular level

**Proliferation**

**Migration**

**Gliogenesis**

e.g. cortical neurons (FGF18)

# The Multiple roles of FGF in neural development

**Neural induction**

**Neural patterning (posterior fates)**

**Regionalization of the neural plate (organizing centers)**

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## At a cellular level

Gliogenesis
Migration
Proliferation
Synaptogenesis
Axon extension/pathfindings
Survival
Differentiation

# The Multiple roles of FGF in neural development

Neural induction

Neural patterning
(posterior fates)

Regionalization
of the neural plate
(organizing
centers)

Specification
of cortical areal identities

Generation of
specific types
of neurons

Differential growth
of cortical subdomain

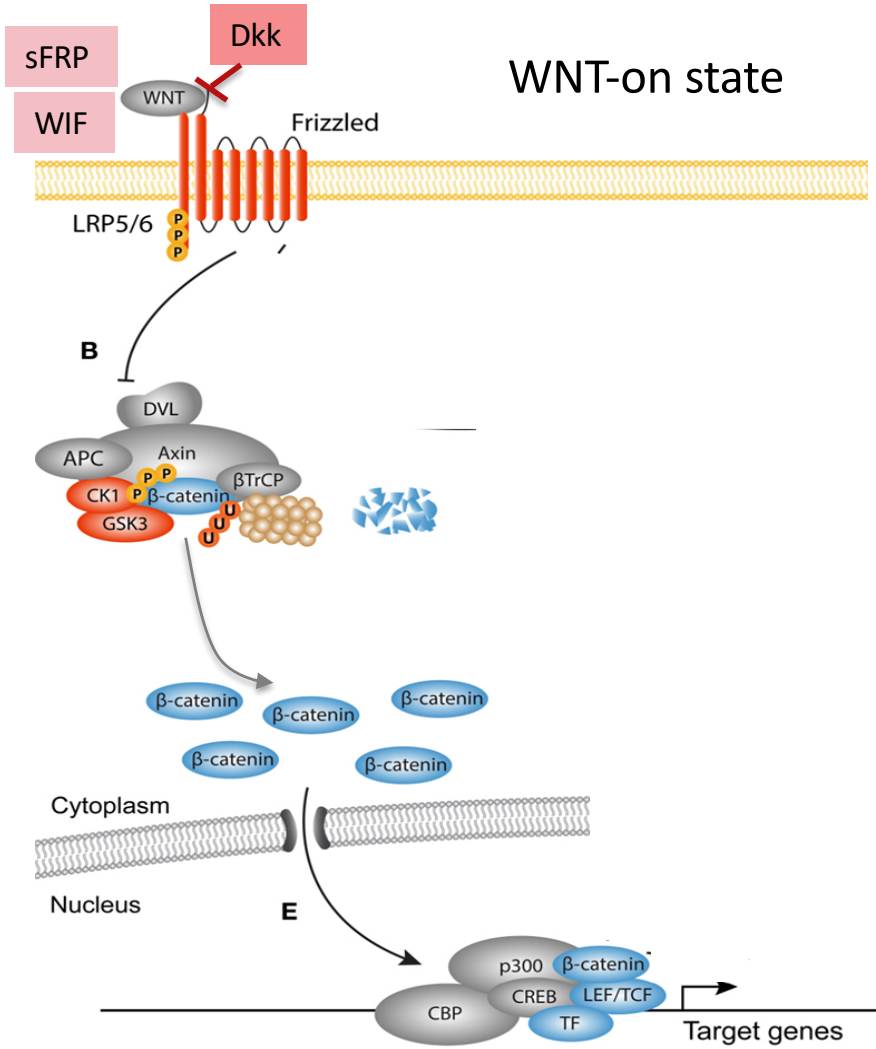
# The Multiple roles of FGFs in neural development

- *Target proliferating progenitors and differentiating neurons*
- *Vast number of FGF ligands → diverse biological responses*
- *Sequential involvement of FGF signals in multiple steps of development*

*of the same territory …the response to the same FGF signal can vary across space and time (e.g. FGF8)*

- *Crosstalk with other signaling pathways*

# WNT Signaling




Modified from Piersma et al., Front. Med., (2015)

Extracellular Matrix

Canonical

**Wnt** binds to Frizzled (Fz) and low-density lipoprotein Receptor-Related Protein (LRP5/6) co-receptor

↓

Inhibition of the destruction complex

↓

Accumulation of non-phosphorylated β-catenin

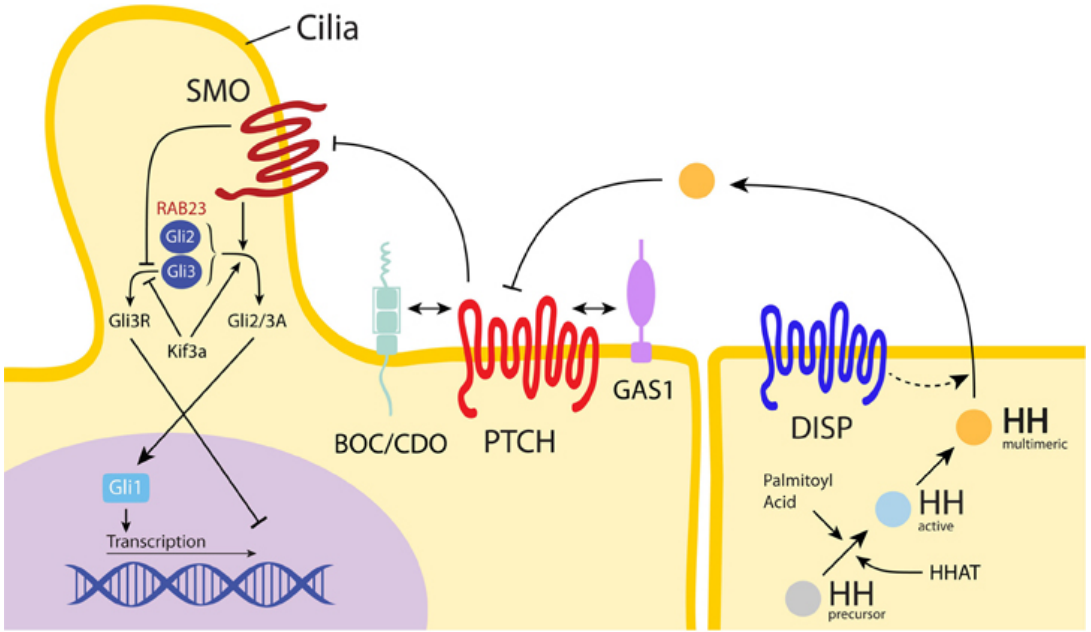
↓

Nuclear translocation and interaction with trascriptional regulators

↓

Wnt target gene expression

# SHH Signaling




Pan et al., Front. Physiol. (2013)

Posttranslational processing of SHH

↓

Secretion of SHH trough Dispatched (DISP)

↓

Binding of SHH to Patched (PTCH)

↓

De-repression of Smoothened (SMO) that moves into the primary cilium

↓

Activation of the Gli trascription factors

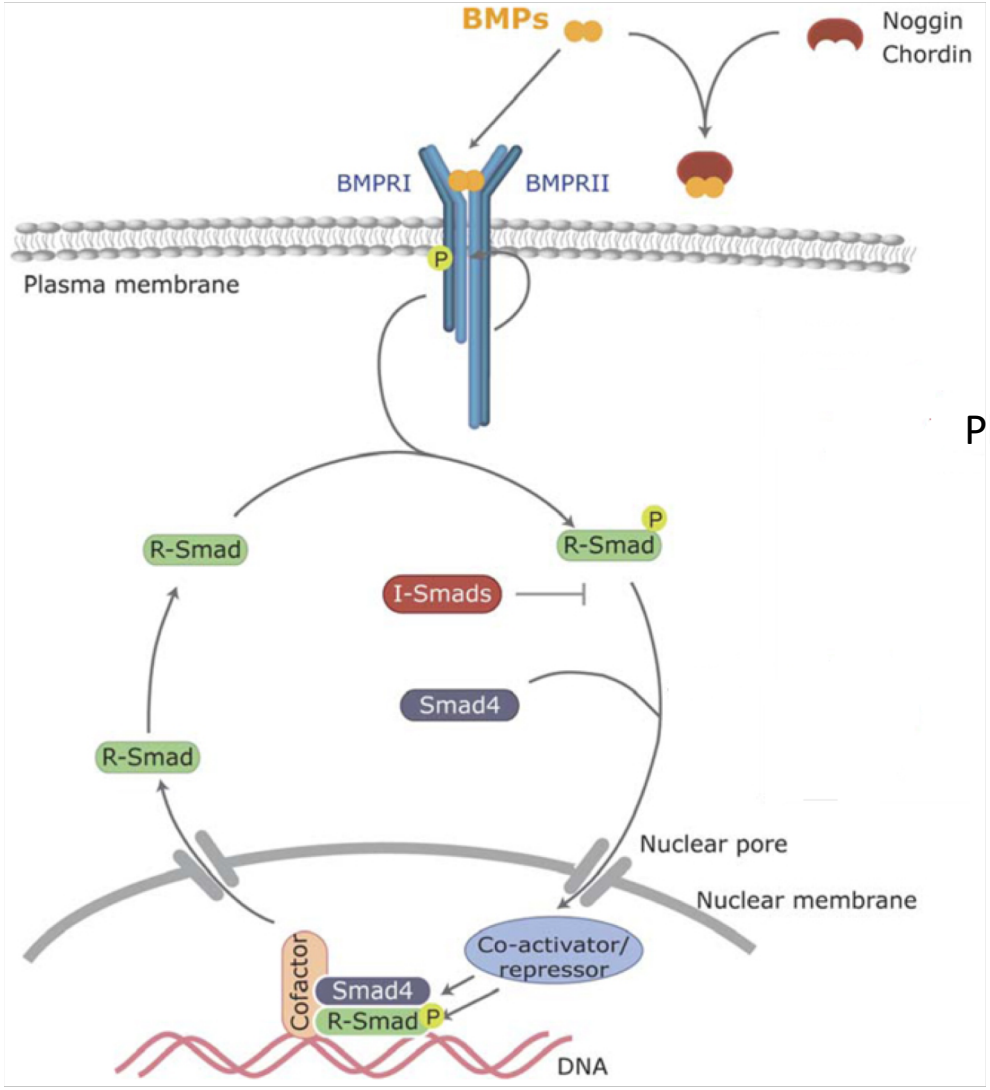
↓

Nuclear translocation

↓

Regulation of gene expression

# BMP Signaling




BMP ligand binds to BMP receptors
when is not sequestered by Noggin/Chordin

↓

BMPRII dimerizes with BMPRI
resulting in its transphosphorilation

↓

Phosphorylation and activation of receptor- regulated
Smad (R-Smad1/5/8)

↓

R-Smads in complex with Co-Smad 4

↓

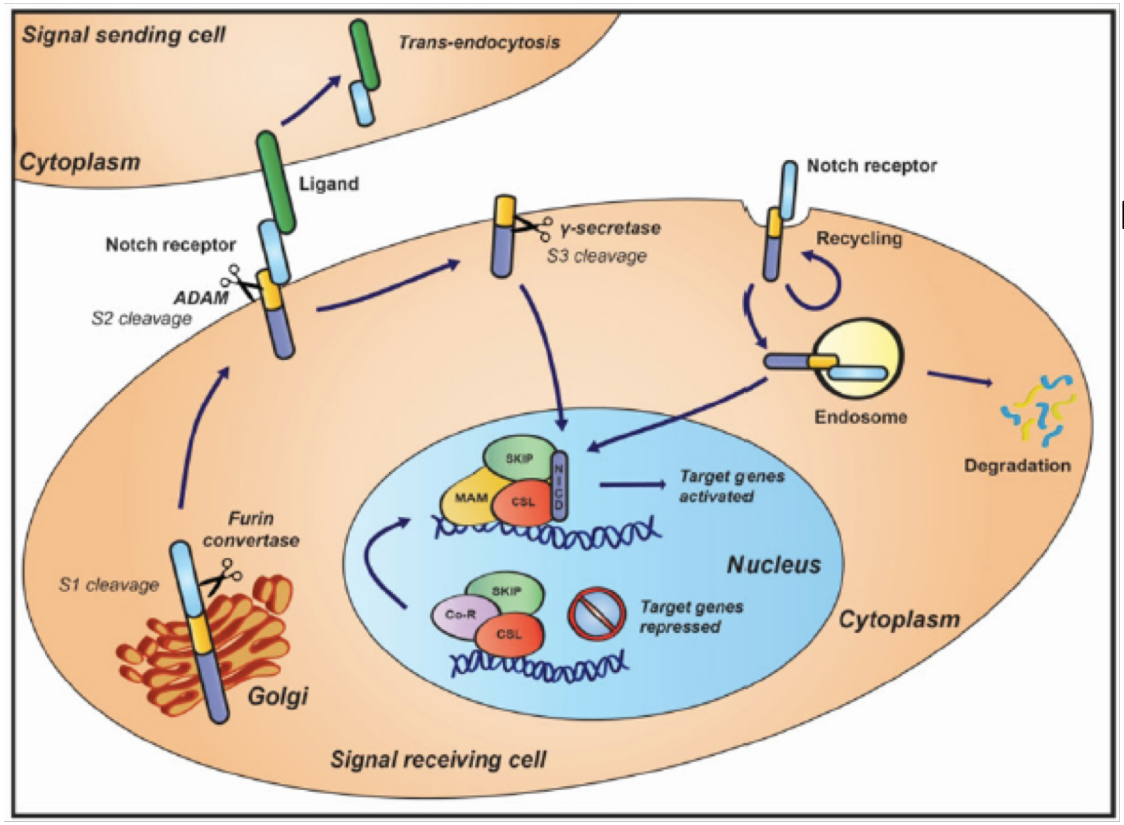
Nuclear translocation

↓

Regulation of gene expression

Gámez et al., Front. Cell. Neurosci. (2013)

# NOTCH Signaling




Carrieri and Dale, Front. Cell Dev. Biol. (2017)

Notch ligand binds to Notch on an adjacent cell

↓

Notch activation and cleavage to liberate Notch intracellular domain (NICD)

↓

Nuclear translocation of NICD

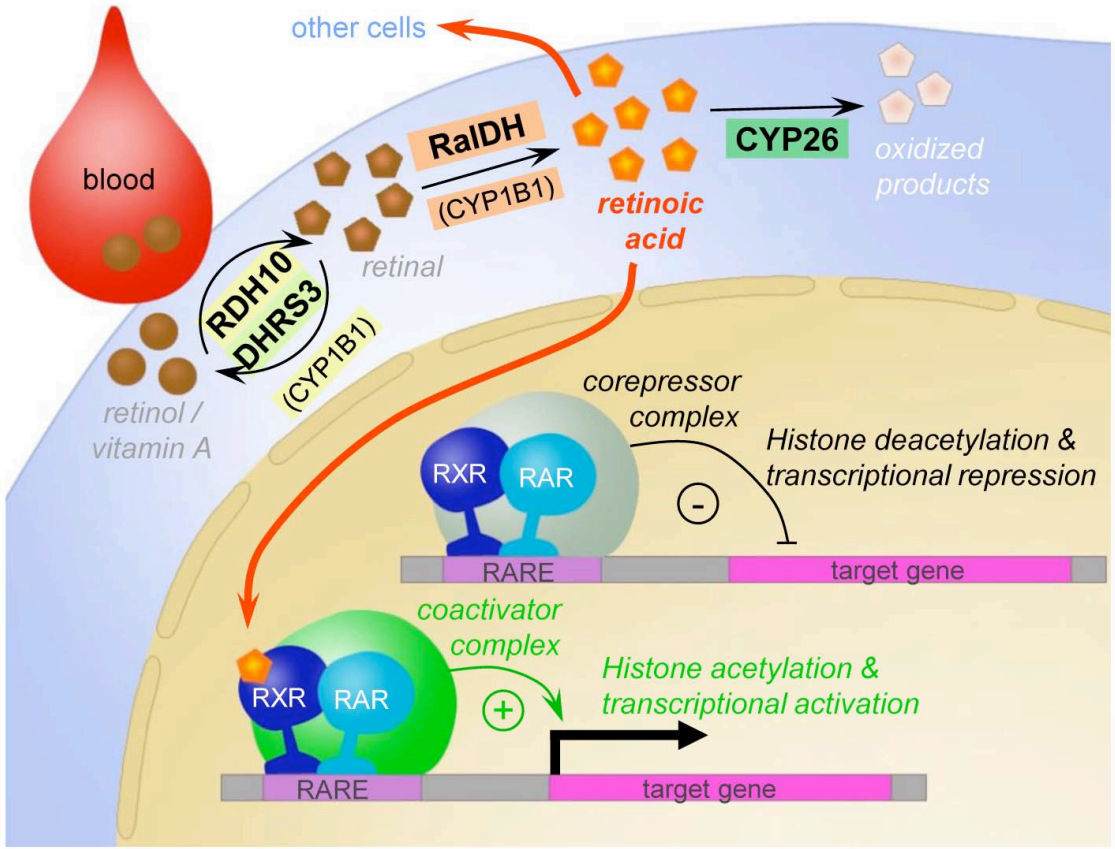
↓

Interaction with CSL,SKIP, MAM…

↓

Regulation of gene expression

# RA Signaling




Roeske et al., PLOS ONE (2014)

Retinoic acid (RA) is synthesized intracellularly from circulating retinol/vitamin A

↓

RA reaches the nucleus

↓

RA binds to RA receptors (RARs) and retinoid X receptors (RXRs) heterodimers which are bind to RA-response element (RARE).

↓

RAR/RXRs conformational changes release of co-repressors and recruitment of co-activators

↓

Chromatin remodeling and transcriptional activation

# Concluding Remarks

The same signal can elicit diverse cellular responses depending on:

- the receiving cell type
- the context
- the developmental timing

Crosstalk between signaling pathways allows cells to respond differently to the same signal.

Misregulation of the signaling cascade can lead to malformations and disease.

# Bibliography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- *Carrieri and Dale, Front. Cell Dev. Biol. 2017 (NOTCH)*
- *Roeske et al., PLOS ONE 2014 (RA)*