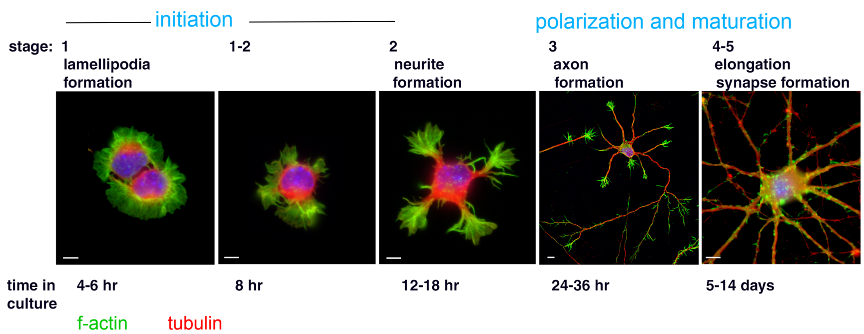
Dendrite growth and branching

Neuronal maturation



- stage 1: "spherical" neuron
- stage 2: neurons extend several neurites
- stage 3: one neurite accelerates its growth rate and matures to form the axon.
- stage 4: dendrites begin to elongate and branch
- stage 5: synaptogenesis

Why is diversity of dendritic arbors important?

- Dendritic arbor must cover its "territory" in order to detect the relevant signals

- Branch pattern and density must be suitable for sampling and processing the signals in the dendritic field

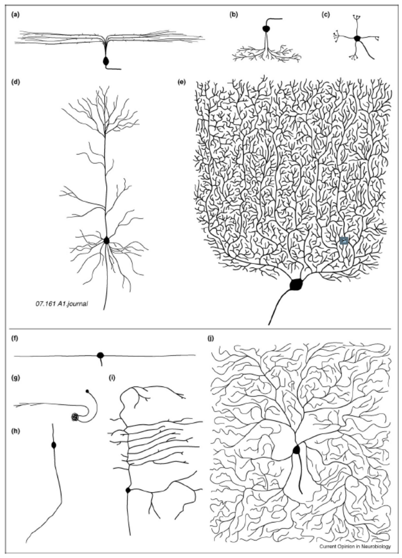
- Dendritic field must have both developmental and mature plasticity in order to respond to changes in the environment.

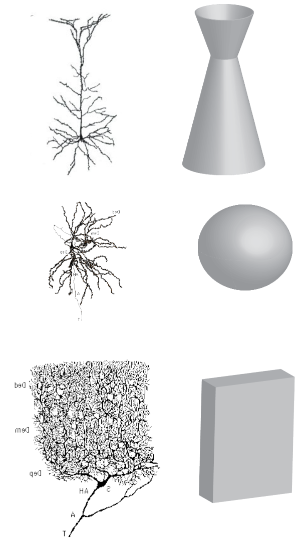
- Subtle differences at dendritic branch points could drastically alter the ability of synaptic input to generate, propagate, and time action potentials (Ferrante et al. 2013)

Dendritic arbors are highly diverse

vertebrate

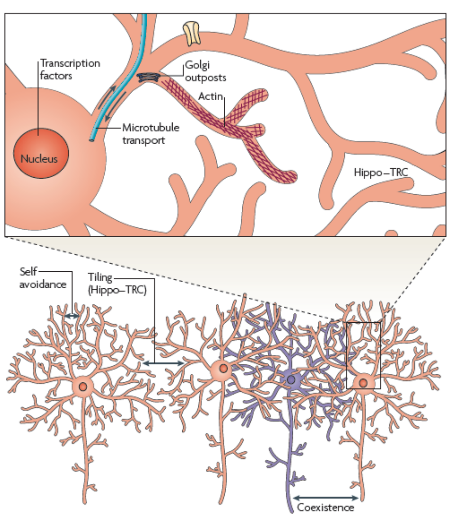
drosophila





Gao, F. B. (2007). Current Opinion in Neurobiology.

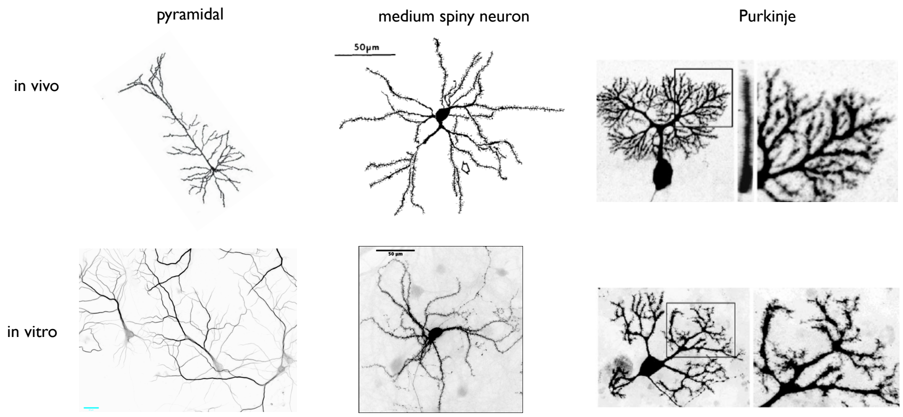
Generally properties of dendritic arbors



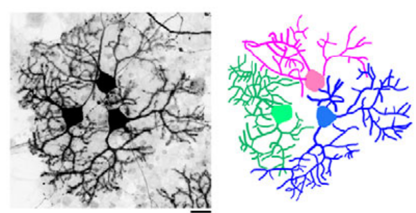
- self-avoidance (branches from the same neuron rarely overlap)
- tiling (avoidance of other neurons of same type) “like-repels-like”
- co-existence with neurons of different types

Jan, Y.-N., & Jan, L. Y. (2010). Nature Reviews Neuroscience, 11(5), 316–328

Basic properties of dendritic arbors are preserved in dissociated cultures, ...



...including self-avoidance and tiling



suggests cell intrinsic and extrinsic properties at work

Genes involved ion dendritic arborization

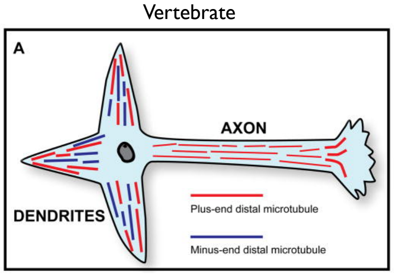
(a very partial list)

- Transcription regulators
  - NeuroD
  - CREB
  - Neurogenin 2
- Secreted proteins & receptors
  - neurotrophins
  - BMP7
  - WNT/Disheveled
  - Sema/plexin/neuropilin
  - netrin/frazzled
  - reelin
- cytoskeleton & regulators
  - rho family
  - gamma-tubulin
- intracellular transport
  - dynein
  - kinesin
- **Secretory pathway and endocytosis**
  - **Golgi outposts**
- RNA targeting and local translation
- **cell proliferation and apoptosis**
  - **Notch**

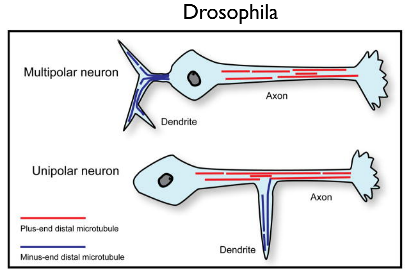
Jan, Y.-N., & Jan, L. Y. (2010). Nature Reviews Neuroscience, 11(5), 316–328

Microtubule polarity may be different in in/vertebrates

Vertebrate



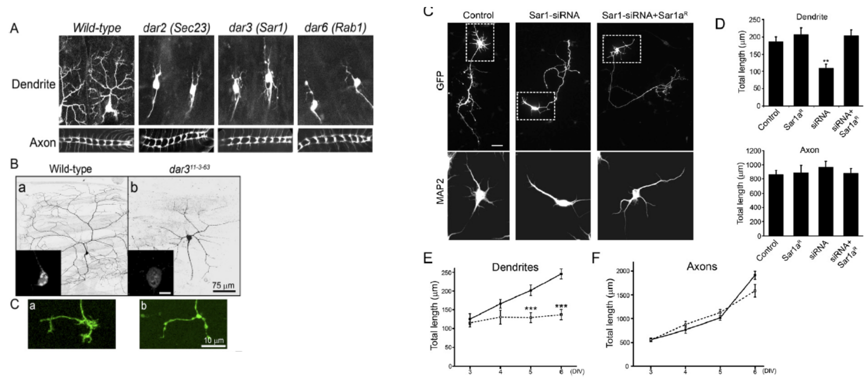
Drosophila



- Microtubule polarity has implications for transport and sorting

Growing Dendrites and Axons Differ in Their Reliance on the Secretory Pathway

Drosophila sensory neurons in vivo | Hippocampal neurons in culture



- Mutation/knockdown of genes involved in ER to Golgi transport mediated by COPII vesicles reduces dendrite, but not axon growth

Ye at al. (2007) Cell 130, 717–729

ER → Golgi → Plasma membrane trafficking

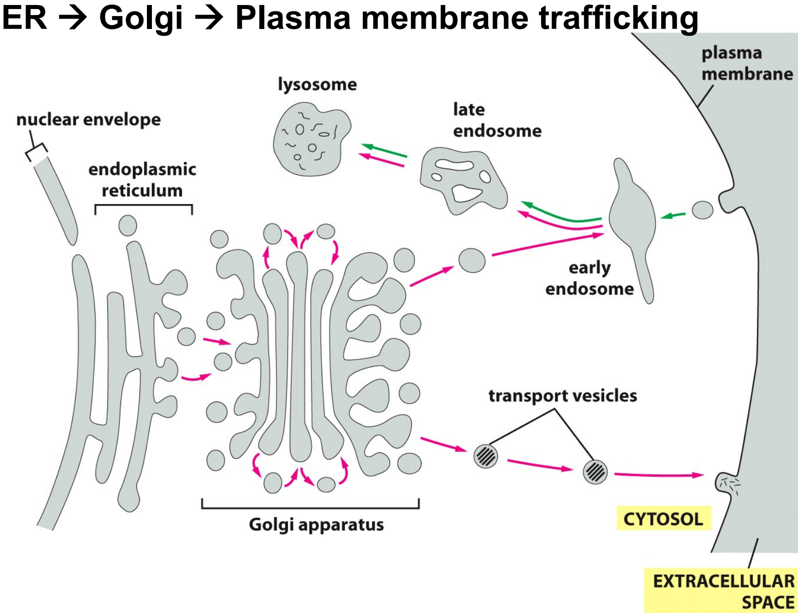
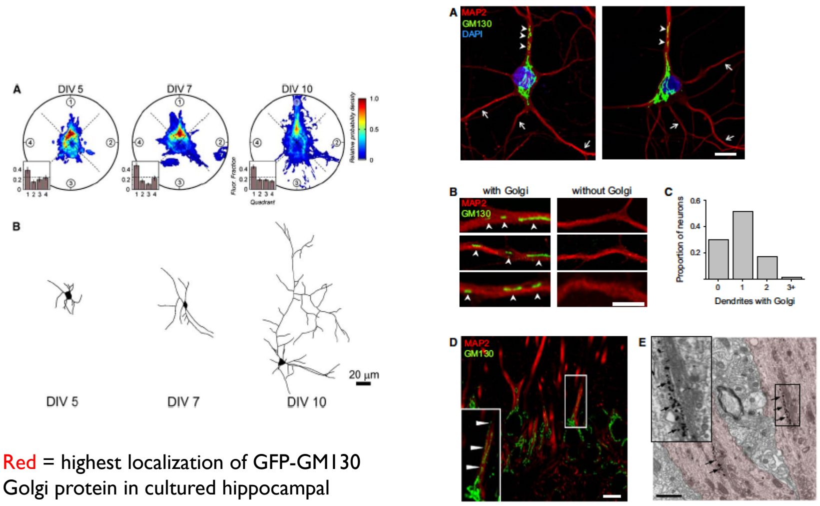


Figure 15-18 Essential Cell Biology 3/e (© Garland Science 2010)

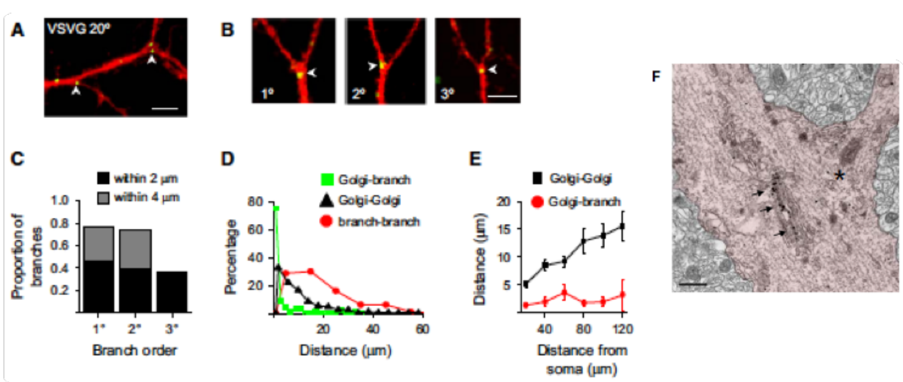
Golgi accumulation defines the apical dendrite in pyramidal neurons



Red = highest localization of GFP-GM130 Golgi protein in cultured hippocampal neuron

Horton et al. (2005) Neuron Vol. 48, 757–771

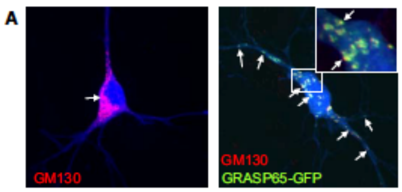
Golgi outposts accumulate at dendrite branch points



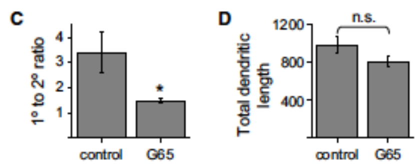
cultured hippocampal neuron

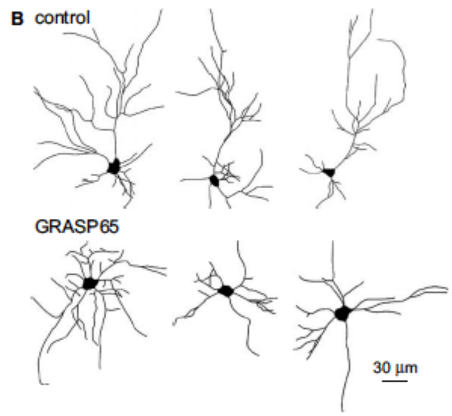
Horton et al. (2005) Neuron Vol. 48, 757–771

Disruption of Golgi outposts alters dendrite polarity and arborization



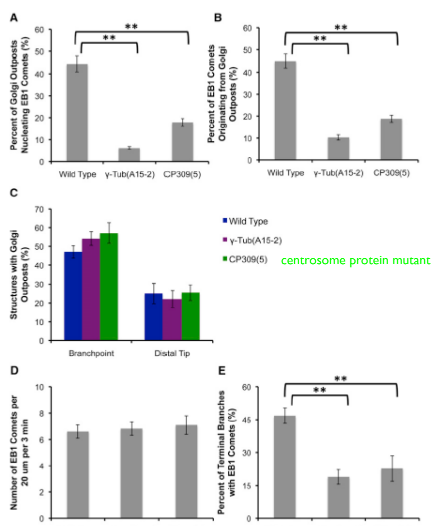
Over-expression of a fragment of the Golgi protein GRASP65 disrupts the Golgi

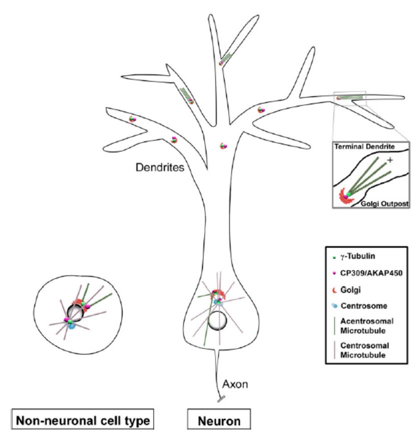




Horton et al. (2005) Neuron Vol. 48, 757–771

Golgi outposts contain gamma tubulin and act as sites of acentrosomal microtubule nucleation

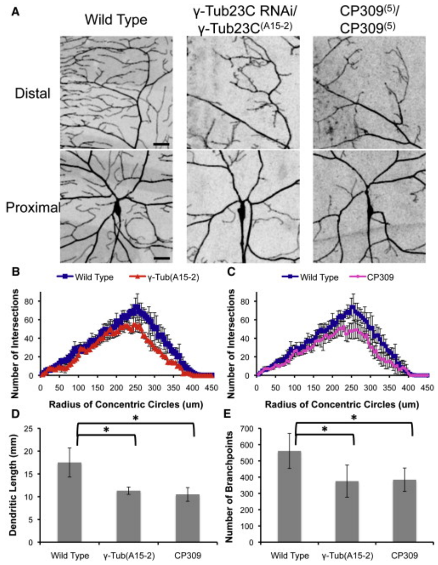


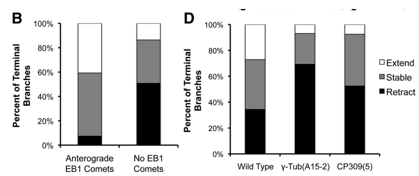


Ori-McKenney (2012) Neuron 76, 921–930,

cultured hippocampal neuron

Acentrosomal microtubule nucleation promotes distal dendrite branching and stability

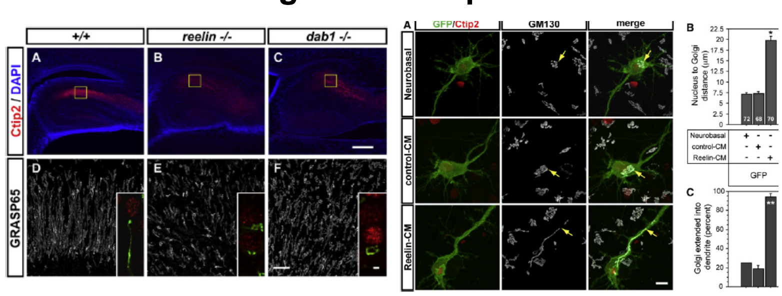


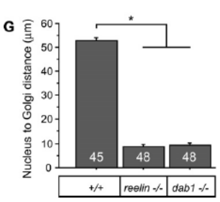


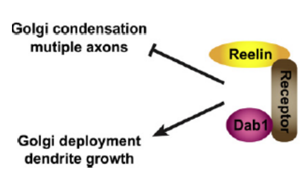
- Dendrite branches are more likely to extend if they have acentrosomal microtubule nucleation (as determined by EB1 comets)

Ori-McKenney (2012) Neuron 76, 921–930,

Reelin and Dab1 regulate the distribution of Golgi into the apical dendrite



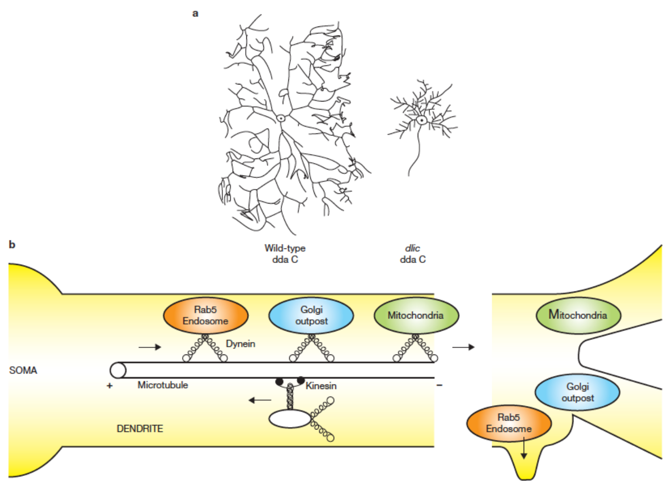




Ctip2 = CA1, layer V pyramidal neurons
GRASP65 = Golgi marker

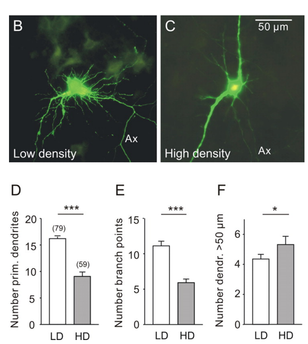
Matsuki, et al(2010) Cell.

Dendrite elongation depends on microtubule based transport



- Dynein mutant has shorter dendrites, but still has lots or branches
- Could this be due to an energy deficit?

Cell density affects dendrite morphology



LD = 15,000-30,000 cells/cm2

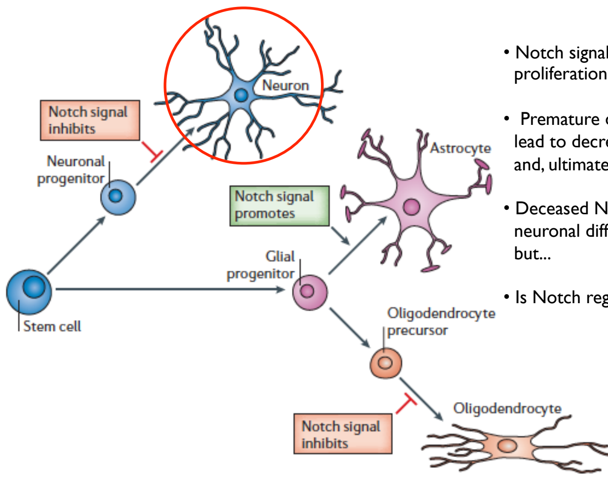
MD = 50,00 cells/cm2

HD = 150,000 cells/cm2

@ High density (HD), neurons have fewer, less branched, but longer dendrites compared to low density (LD)

Patricia Salama-Cohen et al. Mol. Biol. Cell 2005;16:339-347

Notch signaling: cell-cell signaling proliferation, neurogenesis and beyond...

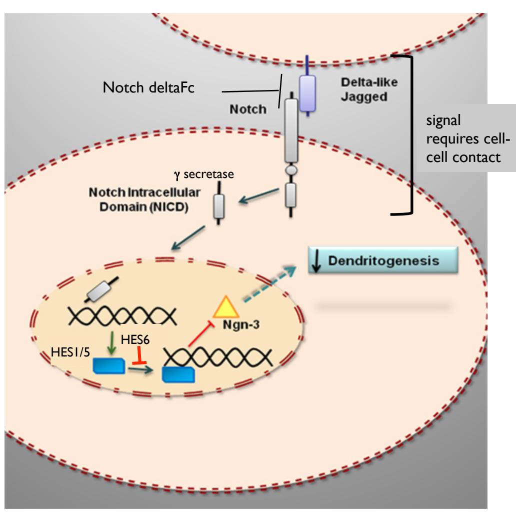


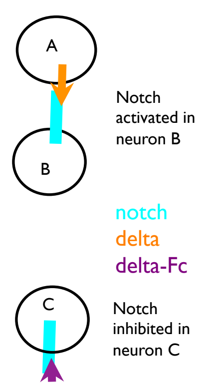
- Notch signaling is important for proliferation of neural progenitors
- Premature decrease in notch signal can lead to decreased number of progenitors and, ultimately, fewer neurons, but .....
- Deceased Notch signaling is required for neuronal differentiation and maturation, but...
- Is Notch regulating dendritogenesis?

Louvi, & Artavanis-Tsakonas, (2006). Nature Reviews Neuroscience, 7(2), 93–102

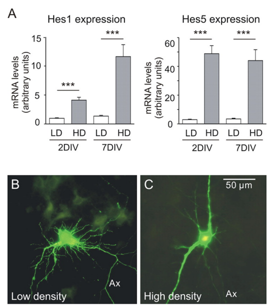
Notch signaling:

notch → NCID → nucleus → increase HES1/5 transcription (bHLH protein) → decrease Ngn3 expression





Cell density affects dendrite morphology via Notch signalling to HES1/5

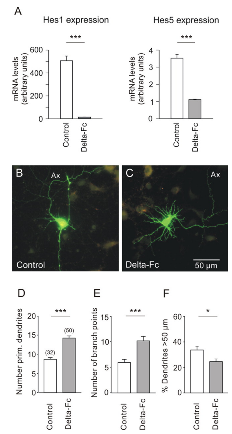


LD = 15,000 cells/cm2

MD = 50,00 cells/cm2

HD = 150,000 cells/cm2

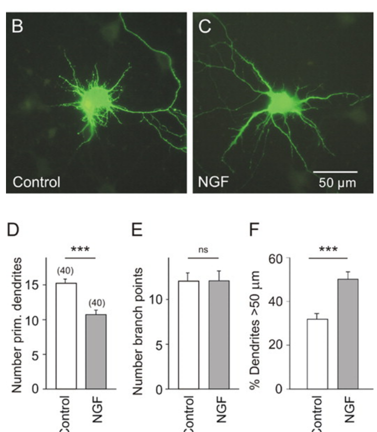
@ HD, neurons
• have fewer, less branched but longer dendrites
• express more HES1/5
• suggest that cell density "regulates" HES expression

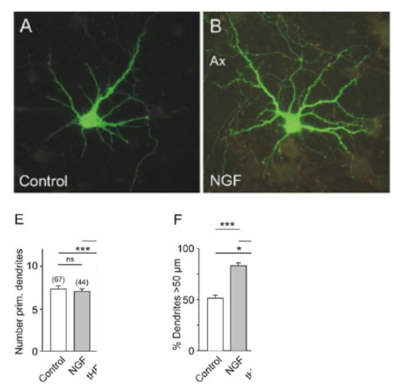


@ MD, inhibition of Notch signaling
• reduces HES1/5 expression
• neurons have more dendrites that are more branched
• make neurons look more like LD
• suggests that HD may increase notch signalling

Patricia Salama-Cohen et al. Mol. Biol. Cell 2005;16:339-347

The effect of NGF depends on neuronal density



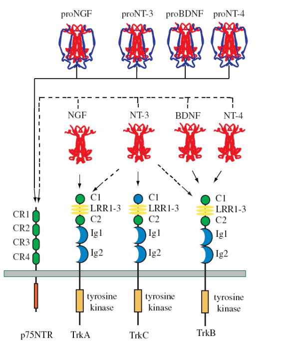


@ LD NGF:
- decreases the number of primary dendrites
- does not change the number of branches
- increases the length of dendrites
- makes neurons more like HD

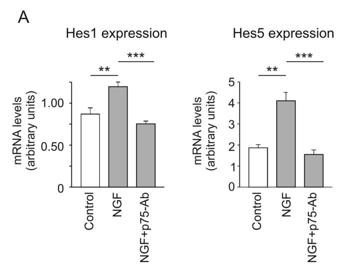
@ MD NGF:
• does not change the number of primary dendrites or branches
• increases the length of primary dendrites & branches
• makes neurons more like HD

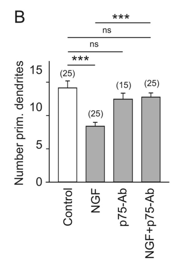
Salama-Cohen, P. (2004). Mol Biol Cell, 16(1), 339–347 cultured hippocampal neuron Salama-Cohen, et al. (2006).. Journal of Neurochemistry, 97(5), 1269–1278.)

NGF induction of HES1/5 expression is dependent on the p75 receptor



Reichardt Phil. Trans. R. Soc. B (2006) 361, 1545–1564

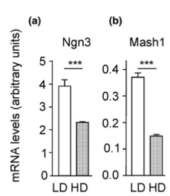


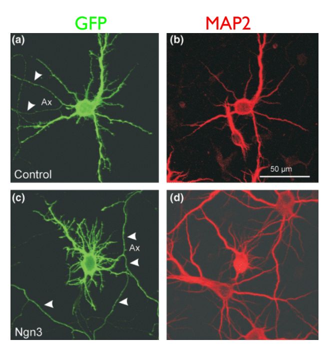


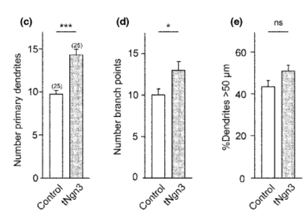
@ LD NGF:
- increases HES1/5 expression
- decreases # of primary dendrites
- effect of NGF is blocked by function-blocking Ab to p75

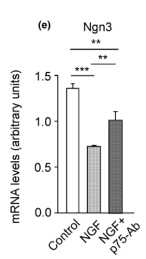
Patricia Salama-Cohen et al. Mol. Biol. Cell 2005;16:339-347

NGF treatment or high density reduce expression of neurogenin 3 (Ngn3)







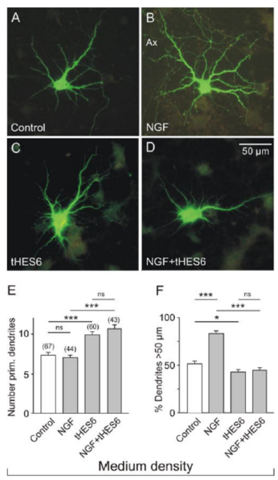


@ HD:
- Ngn3 expression is reduced

@MD
- NGF reduces Ngn3 expression
- Ngn3 over-expression
  - increases # of primary dendrites and branches
  - does not change length of primary dendrites
  - makes neurons look like LD
- suggests that NGF/HD oppose the effects of Ngn3

Journal of Neurochemistry Volume 97, Issue 5, pages 1269-1278, 15 MAR 2006 DOI: 10.1111/j.1471-4159.2006.03783.x

The effect of NGF is blocked by over-expression of HES6

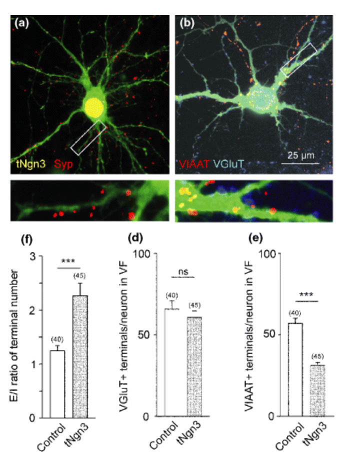


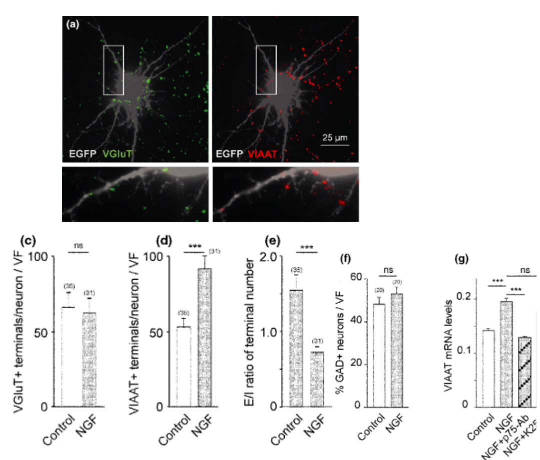
@ MD:

- NGF increases the length, but not the number of primary dendrites & branches (similar to HD)
- Overexpression of tHES6 increases the number of primary dendrites, but not the length (more like LD)
- Overexpression of HES6 blocks the effect of NGF on dendrite length
- Suggests that NGF and HES6 have <u>opposing</u> functions in dendritogenesis

Salama-Cohen, P. (2004). Mol Biol Cell, 16(1), 339–347 cultured hippocampal neuron Salama-Cohen, et al. (2006).. Journal of Neurochemistry, 97(5), 1269–1278.)

Notch and NGF/p75NTR control the number of inhibitory synapses through Neurogenin 3





@ MD Ngn3 overexpression (dendrites more like LD):

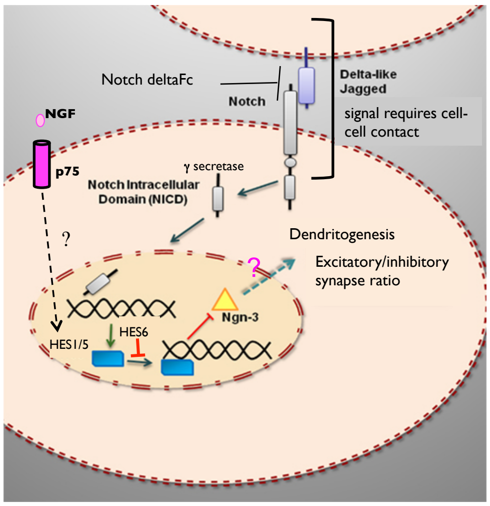
- does not change the number of excitatory synapses
- <u>decreases</u> the # of inhibitory synapses

@ MD NGF (dendrites more like HD):

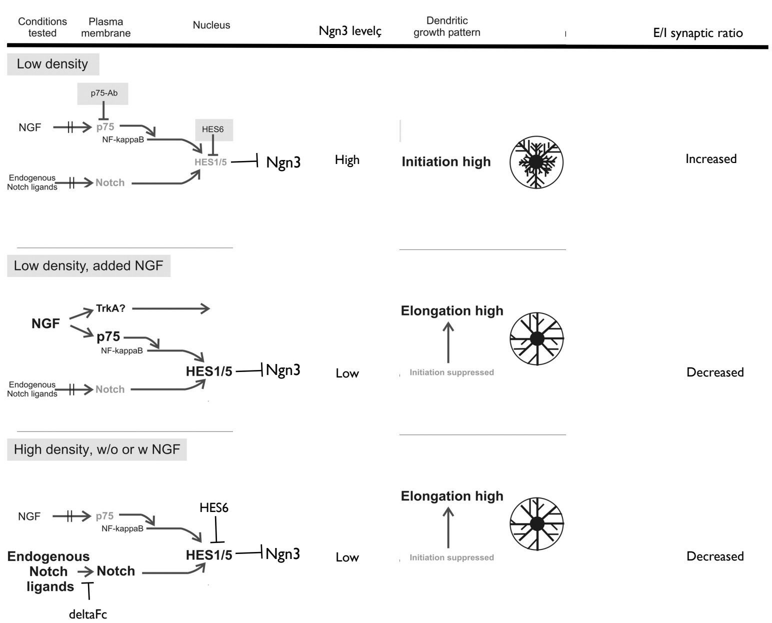
- does not change the number of excitatory synapses
- <u>increases</u> the # of inhibitory synapses

Journal of Neurochemistry Volume 97, Issue 5, pages 1269-1278, 15 MAR 2006 DOI: 10.1111/j.1471-4159.2006.03783.x

Notch signaling:



- Notch signaling,
  - increased at HD
  - reduces dendrite branching
  - increases primary length
  - increase # of inhibitory synapses
- NGF signaling 'mimics' notch signal
- Both Notch and NGF
  - increase HES1/5
  - decrease Ngn3
- Ngn3
  - increases dendrite branches
  - does not change length of primary dendrites
  - decreases # of inhibitory synapses
  - Ngn3 is a transcription factor...what is it regulating???



Patricia Salama-Cohen et al. Mol. Biol. Cell 2005;16:339-347

How is dendritic arborization regulated by cell density? Developmental homeostasis and excitability levels

- cell density = chance of cell-cell contact
- cell-cell contact required for notch signaling
- Notch signalling induces HES1/5 (bHLH transcription factor) expression
- HES1/5 inhibits expression of Ngn3
- Alterations in branch patterns can affect the relative excitatory/inhibitory balance
- What is the relationship between the number and length of branches?
- Why would is an increase in the total "amount" of dendrite (i.e. more and/or longer) correlated with increased excitability?
- Would pharmacological alteration of NMDA or GABA-A receptors affect dendrite arborization. In what direction?

Growth of dendrites

- Compared to axon growth and branching, dendrite growth and branching is:
  - regulated by an overlapping, but distinct set of molecules
  - much more dependent on the secretory pathway
- Neuron types with polarized dendrites (e.g. pyramidal neurons) may be dependent on Golgi accumulation to develop polarity
- Golgi outposts may provide sites of acentrosomal microtubule nucleation that are especially important for distal branching
- Notch signaling provides cell-cell signaling that acts as a "density sensor"
  - regulates dendrite elongation and branching
    - high notch signal → cell has short highly branched dendrites
    - *in vitro* high NGF mimic the effects of notch, presumably because *in vivo* high NGF would only be achieved at high cell density