Dendrite growth and branching

Neuronal maturation

<table>
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<tr>
<th>Stage</th>
<th>Description</th>
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<td>Lamellipodia formation</td>
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<tr>
<td>1-2</td>
<td>Neurite formation</td>
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<td>3</td>
<td>Axon formation</td>
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<td>4-5</td>
<td>Elongation and synapse formation</td>
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- 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

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

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

...including self-avoidance and tiling

suggests cell intrinsic and extrinsic properties at work
Dendrite growth and branching

Genes involved in dendritic arborization
(a very partial list)

- Transcription regulators
  - NeuroD
  - CREB
  - Neurogenin 2
- Secreted proteins & receptors
  - neurotrophins
  - BMP7
  - WNT/Dishevelled
  - 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


Microtubule polarity may be different in in/vertebrates

- Microtubule polarity has implications for transport and sorting
Growing Dendrites and Axons Differ in Their Reliance on the Secretory Pathway

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

Ye et al. (2007) Cell 130, 717–729

ER → Golgi → Plasma membrane trafficking

Figure 15-18 Essential Cell Biology 3rd (© Garland Science 2010)
Golgi accumulation defines the apical dendrite in pyramidal neurons

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

Golgi outposts accumulate at dendrite branch points
Dendrite growth and branching

Disruption of Golgi outposts alters dendrite polarity and arborization

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

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


Ori-McKenney (2012) Neuron 76, 921–930,
Dendrite growth and branching

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)

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

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

Dendrite growth and branching

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

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

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 ....
- Decreased Notch signaling is required for neuronal differentiation and maturation, but ...
- Is Notch regulating dendritogenesis?

Notch signaling:

notch $\rightarrow$ NCID $\rightarrow$ nucleus $\rightarrow$ increase HES1/5 transcription (bHLH protein) $\rightarrow$ decrease Ngn3 expression
Cell density affects dendrite morphology via Notch signalling to HES1/5

@ 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

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

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

[Images and text from the document]
The effect of NGF is blocked by over-expression of HES6

- NGF increases the length, but not the number of primary dendrites & branches (similar to HD)
- Overexpression of HES6 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 opposing functions in dendritogenesis

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
  - decreases the # of inhibitory synapses
- MD NGF (dendrites more like HD):
  - does not change the number of excitatory synapses
  - increases the # of inhibitory synapses
Dendrite growth and branching

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??

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 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