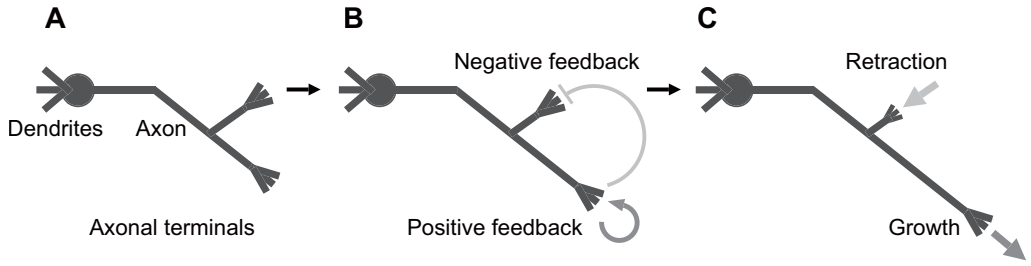

Fig. 1. Differential growth control of axonal branches in a single arbor. (A) A neuron that possesses a branched axon with two terminals. (B) It is hypothesized that signals acting positively on a particular process may negatively affect neighboring processes. (C) These signals may cause differences in process growth and retraction rates and coordinate the axonal arbor shape.

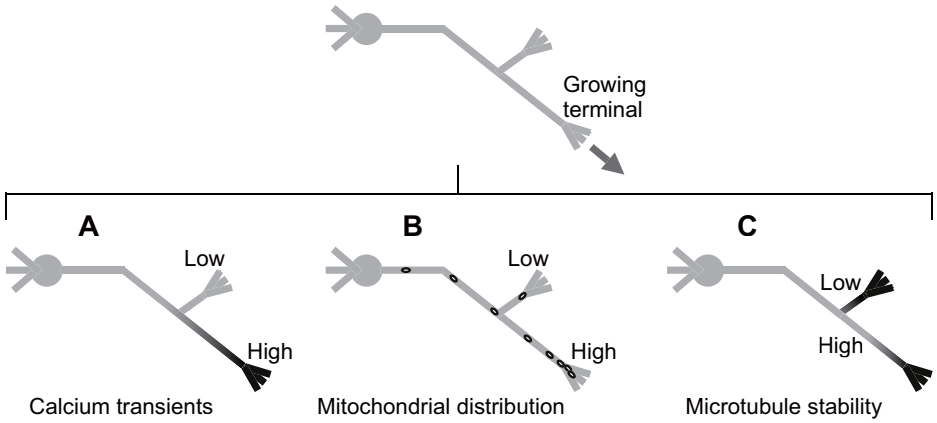

Fig. 2. Process-dependent differences that contribute to differential growth. (A) A growing terminal process exhibits higher Ca^{2+} transients than a neighboring branch that extends less. (B) Mitochondria are preferentially sorted into a growing process. (C) Microtubule stability is higher in longer processes than in shorter neighboring processes, which causes posttranslational modification differences.

The axonal branches of isolated hippocampal neurons alternate periods of growth; when one side of the branch actively grows, the other remains quiescent. The growth and quiescent states of a branch switch after a few hours [10]. These observations suggest that within a single axonal arbor, growth and retraction can be regulated in branch-dependent manner. Intriguingly, studies using isolated cortical neurons have shown that activation of growth on one side branch increases the retraction rate of another branch [12]. Thus, it can be hypothesized that there are mechanisms that maintain the growth of particular axonal branch during a period of time and that simultaneously send negative signals to neighboring branches to enhance their retraction (Fig. 1). As described below, recent studies have demonstrated that certain intracellular events (i.e., calcium signaling, mitochondrial sorting, and microtubule regulation) participate in this cellular function and contribute to the differential growth or retraction of an axonal branch.

2.2 Calcium transients

Calcium (Ca^{2+}) signals play pivotal roles in controlling dendritic and axonal morphology [13,14]. Entry of Ca^{2+} from voltage-dependent Ca^{2+} channels locally enhances branch growth [15,16]. Using Ca^{2+} imaging in branched axons of cortical neurons, Hutchins and Kalil [12,15] found that these neurons exhibit spontaneous localized calcium transients. In their system, primary axons exhibit more rapid outgrowth than collateral branches do. Intriguingly, local Ca^{2+} transients frequently occur in a primary axon but not in its collateral branches, and the frequency of Ca^{2+} transients positively correlates with the growth rate of axonal terminals [12] (Fig. 2A). Different frequencies of Ca^{2+} transients are thought to be involved in the differential control of terminal growth and retraction. When Bay K8644, an agonist for the L-type voltage-dependent Ca^{2+} channel, is applied in culture, it enhances localized Ca^{2+} transients and the differential growth of processes. By contrast, application of nifedipine, an antagonist at this same Ca^{2+} channel, blocks both localized Ca^{2+} transients and differential growth. Furthermore, induction of local Ca^{2+} transients by using caged Ca^{2+} increases growth of UV-stimulated axonal processes, whereas it causes retraction of unstimulated processes [12]. Downstream signaling molecules, such as calcium/calmodulin-dependent protein kinase II is thought to be involved [15]. However, the mechanisms whereby the outgrowth of one side of a branch inhibits the extension of a neighboring process remain undetermined.

2.3 Mitochondria distribution

In animal cells, mitochondria play a major role in ATP synthesis. In addition, these organelles are involved in calcium signaling and apoptotic signals [17,18]. Within axons, mitochondria are sparsely distributed throughout the arbor, but they are enriched in areas in which energy consumption is high as compared with other regions, such as synapses and nodes of Ranvier [19–21]. The microtubule motors ki-