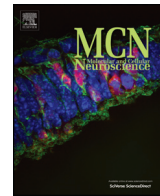




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It takes a village to raise a branch: Cellular mechanisms of the initiation of axon collateral branches

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ABSTRACT

The formation of axon collateral branches from the pre-existing shafts of axons is an important aspect of neurodevelopment and the response of the nervous system to injury. This article provides an overview of the role of the cytoskeleton and signaling mechanisms in the formation of axon collateral branches. Both the actin filament and microtubule components of the cytoskeleton are required for the formation of axon branches. Recent work has begun to shed light on how these two elements of the cytoskeleton are integrated by proteins that functionally or physically link the cytoskeleton. While a number of signaling pathways have been determined as having a role in the formation of axon branches, the complexity of the downstream mechanisms and links to specific signaling pathways remain to be fully determined. The regulation of intra-axonal protein synthesis and organelle function are also emerging as components of signal-induced axon branching. Although much has been learned in the last couple of decades about the mechanistic basis of axon branching we can look forward to continue elucidating this complex biological phenomenon with the aim of understanding how multiple signaling pathways, cytoskeletal regulators and organelles are coordinated locally along the axon to give rise to a branch.

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1. Introduction

The function of the nervous system requires complex neuronal circuitry. The formation of circuitry depends on the establishment of synaptic contacts between single neurons and multiple targets. During development, axon branching allows each neuron to establish synaptic contacts with multiple targets and is crucial for the assembly of highly interconnected network (Gallo, 2011; Gibson and Ma, 2011; Lewis et al., 2013; Rockland, 2013; Kalil and Dent, 2014; Petrovic and Schmucker, 2015). Therefore, understanding the mechanisms underlying the control of axonal branching is crucial in the study of neuronal circuit development (Gibson and Ma, 2011). In the adult nervous system axon branches also emerge in response to injury and neurodegeneration, and are repressed by extracellular signals (Onifer et al., 2011; Akbik et al., 2012; Carmel and Martin, 2014; Kadomatsu and Sakamoto, 2014). The injury induced axon branching/sprouting contributes to the endogenous circuitry repair mechanisms (Carmel and Martin, 2014).

Axon branches can arise from two distinct mechanisms. (1) The growth cone can split and give rise two Y or T shaped axon branches. For example, live imaging of individual zebrafish motor axons reveals that the first axonal branches are generated via bifurcation of the growth cone (Sainath and Granato, 2013). Although growth cone bifurcation can contribute to the formation of branches in specific instances, this is not the major mechanism that contributes to axon branching (discussed in Gallo, 2011). (2) Axon collateral branches emerge from protrusive filopodia and lamellipodia initiated locally along the shaft of the axon independent of the growth cone. Studies of the dynamics of collateral branching revealed three mechanisms of axon collateral branch initiation primarily involving either formation of filopodia, lamellipodia or growth cone pausing (reviewed in Gallo, 2011). In the filopodia based mechanism, branches initiate as axonal filopodia protrusions from the quiescent axon shaft. Time-lapse imaging of fluorescently labeled corticospinal axons showed that in the vicinity of the pons the axon shaft exhibits several dynamic behaviors including the de novo formation of filopodia extensions, and some of the filopodia mature into a branch (Bastmeyer and O'Leary, 1996). Similarly, in vitro studies demonstrated that along the axons of sensory neurons, branches are initiated by the emergence of filopodia followed by stabilization of the filopodia and maturation into a branch (Fig. 1; Gallo and Letourneau, 1998, 1999; Ketschek and Gallo, 2010; Spillane et al., 2012). In the lamellipodial mechanism, branches arise from lamellipodia that form at the base of the axon, and move anterograde along the axon. These lamellipodial precursors of branches are termed growth cone like “waves” and have been observed in hippocampal neurons (Ruthel and Banker, 1999; Flynn et al., 2009). Branches then emerge from locations along the axon where the waves stop. Moreover, lamellipodia can also arise de novo along the axon shaft in the absence of growth cone like “waves”. In the growth cone pausing mechanism, the collateral branch is formed from sites along the axon shaft representative of locations where the growth cone stalled, leaving behind a domain of persistent protrusive activity, followed by resumption of its advance (Halloran and Kalil, 1994; Kalil et al., 2000). The importance of axonal protrusive activity in the form of filopodia and lamellipodia is underscored in all of these mechanisms for the initiation of a collateral branch.

The formation of axon branches involves the regulation of the neuronal cytoskeleton. The major constituents of the axonal cytoskeleton include actin filaments and microtubules that are highly dynamic and undergo rapid cycles of polymerization and depolymerization (Fig. 1;

Gallo, 2011; Kalil and Dent, 2014; Zhang and Rasband, 2016). Branching initiates through the protrusion of actin filament-based filopodia and lamellipodia that are subsequently invaded by axonal microtubules as the branch matures and continues extending (Fig. 1). In this review, we will discuss the role of cytoskeletal dynamics and their regulators in the formation of branches. Moreover, we will consider the signaling pathways known to regulate cytoskeletal dynamics and modulate axonal branching, and conclude with a discussion regarding the necessity to elucidate how the many cellular events underlying branching are coordinated in space and time. The basic sequence of cytoskeletal events and a summary of the identified cytoskeletal regulators underlying the formation of an axon branch at a specific point along the axon shaft are shown in Fig. 1.

2. Cytoskeletal dynamics and reorganization underlying the early stages of branch formation

2.1. Actin dynamics in axonal branching

Unlike the highly dynamic growth cone, the consolidated axon shaft contains relatively low levels of actin filaments and exhibits minimal protrusive activity. The formation of axon branches is preceded by the dynamic polymerization and reorganization of the cytoskeleton along the axon shaft. This includes the local accumulation of actin filaments that is required for the formation of actin-driven protrusions and subsequent branch formation. The first step in the formation of collateral branches involves the actin filament dependent initiation of axonal filopodia, and in some cases lamellipodia (as discussed above). Since the formation of axonal filopodia is the most common first step for branching, this review will focus on this process. Filopodia are thin finger like membrane protrusions mainly composed of a bundle of parallel actin filaments and actin associated proteins. The rapidly polymerizing barbed ends of filaments are oriented toward the tip of the filopodium, generating forces that push the membrane forward. Formation of filopodia can be understood in terms of three basic events: actin filament nucleation driving the initiation of new actin filaments, rapid elongation of nucleated actin filaments through barbed-end polymerization, and the bundling of elongating actin filaments (Svitkina et al., 2003; Mattila and Lappalainen, 2008).

2.1.1. Axonal actin patches serve as precursors to the emergence of axonal filopodia

Focal accumulations of actin filaments along the axon, termed actin patches, are precursors to the emergence of filopodia (Figs. 1A–C, 2A; reviewed in Gallo, 2011, 2013), a form of filopodial emergence that is similar to that described for filopodia arising from non-neuronal lamellipodia (Svitkina et al., 2003). Actin patches consist of localized highly dynamic domains of actin filaments with general organization similar to lamellipodial structures (Spillane et al., 2011). Live imaging of chicken sensory neurons transfected with eYFP-actin, revealed that actin patches form spontaneously and are transient (Loudon et al., 2006; Ketschek and Gallo, 2010; Spillane et al., 2011, 2012, 2013; Sainath et al., 2016), and similar structures have been reported in other neuronal systems in vitro and in vivo (Korobova and Svitkina, 2008; Mingorance-Le Meur and O'Connor, 2009; Andersen et al., 2011; Spillane et al., 2011; Chia et al., 2014; Chetta et al., 2015; Hand et al., 2015). Actin patches serving as precursors to the formation of axonal filopodia and branches have also been imaged in vivo (Andersen et al., 2011; Spillane et al., 2011; Hand et al., 2015). Although filopodia emerge from actin patches, only some patches give rise to axonal

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