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# Signaling from plant endosomes: compartments with something to say!

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It is well established in animal systems that compartmentalization of signaling receptors within the endocytic pathway contributes to signaling specificity and regulation (Miaczynska et al. 2004; Fischer et al. 2006). Multiple examples have been reported in vertebrates that demonstrate this concept. Epidermal growth factor receptor (EGFR) is found at the plasma membrane, but when clathrin-mediated endocytosis is impaired, downstream signaling components such as mitogen-activated protein kinases (MAPKs) have reduced activity (Viera et al. 1996). In endosomes, EGFR has been shown to interact with other signaling components (Sorkin et al. 2000). In fact, treatment with a chemical that causes the internalization of inactive (dephosphorylated) ligand-bound receptors, followed by chemical washout, reveals that the endosomal pool of EGFRs is able to promote signaling and a biological response (Pennock and Wang 2003). As important, the plasma membrane and endosomal pools of EGFR appear to be functionally distinct in that the pools show selectivity in their association with other signaling components (Burke et al. 2001). Other examples of active receptor association with endosomes include nerve growth factor association with its receptor TrkA and phospholipase C (Grimes et al. 1996) and the G-protein-coupled  $\beta_2$ -adrenergic receptor (Daaka et al. 1998). The TGF- $\beta$  receptor forms heteromeric complexes that undergo endocytosis and phosphorylation. This endosomal complex in turn phosphorylates and activates the transcription factor R-Smad2, which is targeted to the nucleus. A central modulator of endosomal signaling appears to be SARA (Smad anchor for receptor activation) (Tsukazaki et al. 1998), which serves as an adaptor between the TGF- $\beta$  complex and R-Smad2 (Fig. 1). Endocytosis and endosomal signaling pathways have also been characterized in *Drosophila*, where they are critical for development via the establishment of morphogen gradients and signaling involving endosomal complexes. In *Drosophila*, the TGF- $\beta$ -like morphogen Decapentaplegic (Dpp) is involved in wing disc formation via gradients originating from secretory cells. Endocytosis, as well as

control of extracellular diffusion (via heparin sulfate proteoglycans), contribute to establishment of the intracellular and extracellular components of the gradient, respectively. As with TGF- $\beta$  in vertebrates, a SARA-like homolog has been identified (Bennett and Alpey 2002) and several lines of evidence suggest that Dpp may be involved in signaling that is dependent upon endocytosis and endosomes in a TGF- $\beta$ -analogous manner (Bennett and Alpey 2002; for review, see Fischer et al. 2006).

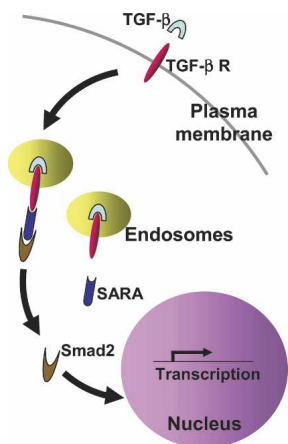
Although there are as many, if not more, endomembrane trafficking components known in plants, the specific involvement of the endocytic pathway in plant receptor signaling has not been well documented. Potential receptors have also been identified. The largest class of plasma membrane receptors (most of which are orphan) appears to be the receptor-like kinases (RLKs), of which there are >600 in *Arabidopsis* and at least 1100 in rice (Morillo and Tax 2006). In spite of this, little is known about trafficking of RLKs, and recent examples in plants have largely pointed toward endocytosis as supporting either the recycling of transporters or as a route for protein turnover.

The small molecule plant hormone, auxin, is essential for many aspects of plant development and response to environmental cues such as light and the directional growth of roots and stems in response to gravity. The movement of auxin is controlled by a family of plasma membrane efflux transporters known as PIN (PINFORMED), whose major role is to establish concentration gradients of auxin across organs that ultimately respond to the hormone via asymmetric growth (Tanaka et al. 2006; Teale et al. 2006; Kerr and Bennett 2007; Zazimalova et al. 2007). For example, differences in lateral growth rates across organs result in the familiar downward bending of roots toward gravity. In roots, the PIN1 transporter is recycled between endosomes and the plasma membrane, and this mechanism along with protein turnover in the vacuole, is thought to be important for establishing and controlling auxin gradients. Moreover, auxin can block endocytosis of PIN1 providing a feedback mechanism, whereby the morphogen itself can influence transporter abundance at the plasma membrane, and thus, efflux and gradient orientation (Paciorek et al. 2005). Interestingly, it is not known in this case

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**Figure 1.** A greatly simplified overview showing the general concept of endosome-mediated signaling. As an example, several elements of TGF- $\beta$  signaling via the endosomal compartment are highlighted. Following ligand (TGF- $\beta$ ; light blue) interaction with a plasma membrane-localized receptor (TGF- $\beta$  R; magenta), the ligand-receptor complex is endocytosed and sequestered during transit in a specific endosome population. In the case of TGF- $\beta$  R, a heteromeric complex is internalized, but is not shown for simplicity. In the endosome (yellow), the cytoplasmic domain of the activated receptor interacts with an adaptor protein (the FYVE protein SARA; dark blue) that mediates interaction with a transcription factor (Smad2; brown). In this example, Smad2 is phosphorylated, leading to its translocation to the nucleus (purple) and activity in transcriptional activation. This general concept is now being discovered in plant systems, indicating that endosomal signaling is an evolutionarily conserved biological mechanism.

what the actual target of auxin is in influencing endocytosis or whether that target is localized to endosomes. In another example of endocytosis, the borate transporter, BOR1, localizes preferentially at the plasma membrane in roots under borate starvation. However, upon reintroduction of borate to the growth medium, BOR1 quickly undergoes endocytosis and targeting to the vacuole for degradation (Takano et al. 2005). As with the auxin transporters, there is no evidence of signaling from endosomes as might be expected in these examples that involve transporters that are recycled. But what about examples of plasma membrane receptors? Fortunately, new ground has been broken.

Brassinosteroids (BRs) are plant polyhydroxylated steroid hormones that are essential for plant growth, differentiation, and development (Vert et al. 2005). Unlike animal steroid hormones, BRs are sensed by a plasma membrane-localized receptor. The RLK BRI1 is known to traffic through endosomes and belongs to a subclass of RLKs known to contain leucine-rich repeats (LRRs). BR interaction with BRI1 also results in heterodimerization (Russeinova et al. 2004) and signaling events leading to the dephosphorylation of the transcription factor BES1 and reduced expression of the BR response genes. Mutants in the *BRI1* gene are extremely dwarfed and completely BR-insensitive.

In this issue of *Genes & Development*, Geldner et al.

(2007) demonstrate that the BRI1 receptor of *Arabidopsis thaliana* is present in several locations. BRI1 is known to be at the plasma membrane; however, colocalization of BRI1-GFP with the endocytic dye FM4-64 and the TGN/endosome marker VHA1-RFP (Dettmer et al. 2006) indicates that BRI1 is at least partially localized in endosomes (Russeinova et al. 2004). The amount of BRI1 in the endosome pool does not increase following treatment of roots with the ligand brassinolide (BL) or even depletion of endogenous BL, indicating that recycling itself is constitutive and not affected by ligand. When the endosomal pool is increased by the application of brefeldin A (BFA), a widely used inhibitor of endosomal trafficking, the result is dephosphorylation of BR-regulated transfer factor BES1 and reduced expression of the early BR-response gene *DWF4*. Pulse-chase indicates that BRI1-GFP is eventually targeted to the vacuole, and BFA blocks this trafficking. The dephosphorylation of endosomal BES1 in cultured roots also occurs with BL, and there appears to be an additive effect when seedlings are treated with both compounds. The results cannot be attributed to changes in BRI1 protein turnover, because half-life experiments indicated no differences in BL-treated and BL-untreated plants. Thus, Geldner et al. (2007) argue that the endosomal pool of BRI1 is functional. This is bolstered by the finding that a YFP fusion of the known BRI1-interacting inhibitory protein BKI1 colocalizes with BRI1-GFP at the plasma membrane and not in endosomes, suggesting that endosomal BRI1 is active in signaling.

The overall results point toward two functionally distinct pools of BRI1: plasma membrane and endosome. Geldner et al. (2007) propose a model in which BRI1 at the plasma membrane may function in binding of a BR ligand. However, it is the endosomal pool that is functional in signal transduction, leading to BES1 activation and transcriptional regulation of *DWF4*. Geldner et al. (2007) put forth the exciting possibility that an as-yet-undefined downstream target is stored in the endosome, then activated directly by an endosomal receptor complex. Such a complex could have analogies to models of TGF- $\beta$  receptor signaling in animals. This report is highly significant in being one of the first examples in plants of ligand-independent trafficking in which a receptor is likely to be active in endosomes after binding ligand at the plasma membrane.

Plants have evolved various approaches to receptor action. Recently, ligand-dependent trafficking of the plant LRR RLK FLS2 was demonstrated (Robatzek et al. 2006). Thus, in plants, as in animals, two types of receptor trafficking have evolved: ligand dependent and ligand independent. One of the great challenges in plant cell biology today is to characterize the numerous endosomal compartments that exist and identify their cargoes and sorting mechanisms. Undoubtedly, when this is accomplished, many facets of plant growth and development will become apparent. Not all decisions are made at the plasma membrane and nucleus! The article by Geldner et al. (2007) is a significant step in providing a framework to begin to unravel the mystery of plant endosomes.

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