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NDR proteins

Lessons learned from Arabidopsis and animal cells prompt a testable hypothesis

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N*myc downregulated* (*NDR*) genes were discovered more than fifteen years ago. Indirect evidence support a role in tumor progression and cellular differentiation, but their biochemical function is still unknown. Our detailed analyses on Arabidopsis NDR proteins (deisgnated NDR-like, NDL) show their involvement in altering auxin transport, local auxin gradients and expression level of auxin transport proteins. Animal NDL proteins may be involved in membrane recycling of E-cadherin and effector for the small GTPase. In light of these findings, we hypothesize that NDL proteins regulate vesicular trafficking of auxin transport facilitator PIN proteins by biochemically alterating the local lipid environment of PIN proteins.

Key words: Arabidopsis Gβγ signaling, N-*myc downregulated* like1, root development, auxin transport, PIN proteins, vesicular trafficking, endocytic recycling

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NDR genes were originally discovered in various differential displays. *NDR* transcripts were found to be elevated during differentiation[1] and in the absence of the transcriptional regulator N-myc mutant background. N and C-myc suppressed *NDR* expression in tumors.[2] NDR proteins are in a subgroup of a superfamily lipases/esterasse containing an α/β hydrolase fold that lack the catalytic triad residues[3] necessary for the hydrolase activity. This suggests that they evolved from a hydrolytic enzyme and have retained the structure but not the functionality of this fold or have developed this molecular architecture for a different yet unidentified purpose. NDR proteins are found in prokaryotes and higher eukaryotes but their mode of action has been unknown until recent work on the plant NDR orthologs.

Recently, human *NDRG1* was identified as a gene responsible for hereditary motor and sensory neuropathy-Lom (HMSNL).[4] *ndrg1*-deficient mice models for HMSNL also indicate that NDRG1 deficiency leads to Schwann cell dysfunction, indicating NDRG1 proteins have a role in the peripheral nervous system, possibly in the Schwann-cell signaling necessary for axonal survival.[5] These finding suggest they might have some important biochemical function as well. NDR1 proteins in animals have also recently discovered as the metastasis suppressors, making them favorite candidates for therapeutic strategies that could increase *NDR* expression to inhibit tumor metastasis.[1,6-11] Recently, Kachhap and co-workers used a prostate cancer cell line to show that NDRG1 is a novel effector for the small GTPase, Rab4a, and is important in recycling E-cadherin in proliferating cells (Kachhap et al. 2007). NDRG1 recruits on recycling endosomes in the trans Golgi network by binding to phosphotidylinositol 4-phosphate and interacts with membrane bound Rab4aGTPase. This finding provides a hint to the possible mechanism for metastasis.

In our recent report in *Plant Cell*, we showed, using Arabidopsis as a model, NDL proteins are novel interactors of the βγ dimer (AGB1/AGG dimers) of the heterotrimeric G protein complex and this G protein-NDR interaction may be evolutionarily-conserved throughout

metazoans since mouse NDRG1 interacts with Arabidopsis AGB1, AGG2.[12]

Arabidopsis *ndl* mutants have phenotypes suggesting that the auxin economy is not normal. Most importantly, altering the level of NDL proteins altered the rate of auxin transport in an AGB1-dependent manner and consequently altered the location and height of local auxin maxima in roots.

Are the discoveries of Arabidopsis NDL proteins operating on auxin transport and the findings in animal cells of NDL proteins involved in membrane cycling pointing us in the same direction on the mechanism of action of NDR action? We believe so.

Recently, it has been shown that the auxin transport facilitators PIN proteins cycle between the endosome and the plasma membrane tonically and that the dynamics (rate and target membrane) is regulated by unknown factors although auxin itself may be directly involved.[13] Small G proteins are central regulators of polarized trafficking of PIN proteins which in turn is critical for auxin flux and direction and the consequent location and size of auxin maxima for development.[14-20] Arabidopsis exchange factors for ARF GTPase GNOM leads to basal targeting of cargoes such as PIN1.[19,21] Other regulators of PIN proteins endocytic recycling includes another ARF GEF (BEN/MIN7),[22] acting at the early endosome, the ARF GAP VAN3,[23] the coat protein clathrin, the actin cytoskeleton, and indirectly microtubules.[14,15,21]

It is not hard to connect the dots here. We hypothesize that NDL proteins, in complex with the 7-transmembrane domain containing membrane protein AtRGS1 and AGB1/AGG dimer and other proteins involved in vesicular trafficking regulate trafficking of auxin transport facilitator PIN proteins by altering the local lipid environment, possibly PIN-containing rafts. This consequently establishes auxin maxima and affects development. Several groups are currently testing this hypothesis.

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