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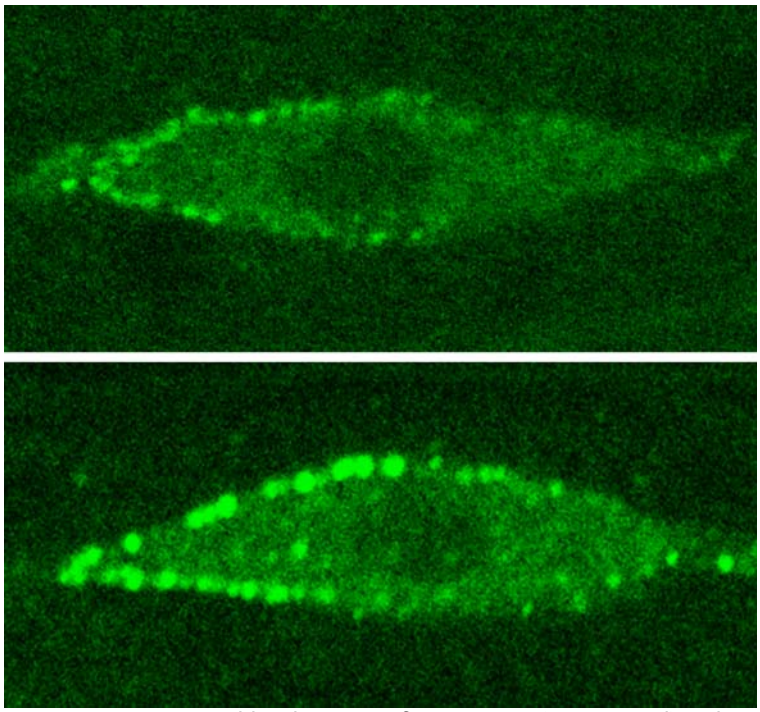
Beta version: New role for cortical WRM-1 in asymmetric cell division

February 23, 2007 – In most species, β-catenin works a double shift, functioning in both cadherin-mediated cell adhesion and at a critical step in the canonical Wnt pathway. But in *C. elegans*, these roles are played by two distinct molecules: HMP-2, which binds cadherin, and WRM-1, which participates in Wnt signaling. The Wnt pathway is critically important throughout roundworm development, regulating the polarity of the majority of asymmetrically dividing cells via the unequal localization of cortical and nuclear factors. The function of WRM-1 at the cellular cortex, however, remains unknown.

Recent work from the Laboratory for Cell Fate Decision (Hitoshi Sawa; Team Leader) is set to change that. In an article published in *Developmental Cell*, Kota Mizumoto, a grad student in the Sawa lab proposes a general model of how cortical WRM-1 interacts with other factors in the Wnt pathway, such as the APC homolog APR-1, to regulate the localization of WRM-1 in the nucleus, where it would otherwise work as a transcriptional activator.



Asymmetric cortical localizations of APR-1::GFP (upper panel) and PRY-1::GFP (lower panel) in the V5.p cell

"The nematode is a really nice system for studying β-catenin in Wnt signaling, because unlike most species, where you have one molecule interacting with both the Wnt pathway and the cadherin machinery, in *C. elegans* you can look at them in isolation," says Mizumoto. "We know that WRM-1 localizes to the anterior cortex and the posterior nucleus during mitosis, and here we tried to work out what role it might be playing there."

The first step toward answering that question came when the team causing WRM-1 to localize throughout the entire cortex, rather than only the anterior, in the T cell lineage that appears in postembryonic development. This strategy involved forcing

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the expression of a fusion protein (WRM-1::GFP::CAAX); in this construct, CAAX effectively tethers WRM-1 to the cortex, while GFP aids in visualization. Worms engineered in this way showed the same phenotype as mutants in which *wrm-1* function is lost (i.e., on division, both daughter cells shared a hypodermal cell fate, in contrast to one hypodermal and one neural cell in wildtype) showing that the defect was an outcome of the uniform localization. Mizumoto further found that LIT-1, the *C. elegans* homolog of MAPK, also localized symmetrically at the cell surface. This is significant, as MAPK has also been shown to play a mediating role in asymmetric cell division.

Given the central role of WRM-1 in Wnt signaling, Mizumoto next looked at APR-1, the homolog of APC, a member of a group of factors that form what is known as the "destruction complex," which marks β-catenin for destruction in the absence of Wnt. In worms in which *apr-1* was knocked down by RNAi, the phenotype was opposite that of the WRM-1::GFP::CAAX mutant; both daughters became neural, not hypodermal. The defect was a mirror image of that of other mutants in which the Wnt/MAPK pathway is upregulated, suggesting that *apr-1* negatively regulates this pathway. Inhibition of *apr-1* also disturbed the pattern of asymmetric WRM-1 nuclear localization, which normally causes it to localize in the posterior nucleus from about the telophase stage of cell division. In the *apr-1* knockdown phenotype, the distribution was symmetric to both nuclei.

***C. elegans* homolog quick reference**

C. elegans	**Familiar**
LIN-44, MOM-2	Wnt
LIN-17	Frizzled
WRM-1	β-catenin (signaling)
LIT-1	MAPK
APR-1	APC
PRY-1	Axin
POP-1	TCF
HMP-2	β-catenin (adhesion)

C. elegans nomenclature differs from that used in many other model organisms.

"It appears that somehow APR-1 enables WRM-1 at the anterior cortex to prevent the accumulation of WRM-1 in the anterior nucleus," says Mizumoto. "When we looked at the movement of WRM-1 out of the nucleus, it appeared that more WRM-1 remains in the nuclei as a result of RNAi knockdown of *apr-1*, which we think has to do with its role as a mediator of nuclear export."

PRY-1, the homolog of Axin, another factor in the destruction complex, also localized asymmetrically to the anterior cortex as did APR-1, suggesting that these may be components of a complex along with WRM-1. This asymmetry failed to occur in Wnt mutants, indicating that the effect is likely regulated by Wnt signaling.

"We still don't have the molecular mechanism that explains the precise way in which APR-1 mediates the inhibition of WRM-1 accumulation in the anterior nucleus by WRM-1 at the anterior cortex," Mizumoto admits, "but we do have a reasonable model of how it might work through the asymmetric export of WRM-1 from the nucleus. But as *apr-1* also appears to be required for the nuclear localization of WRM-1 in other cell types, there may still be some surprises ahead."

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