DEVELOPMENT

Antagonizing fat head

The mechanisms behind the action of Wingless (Wg) and its vertebrate homologue Wnt have slowly been unravelled over the past few years. But there are still surprises. New work published in *Nature* and *Nature Cell Biology* shows that Dickkopf (Dkk), an antagonist of the Wnt pathway, inhibits signal transduction through a completely unsuspected mechanism.

We know that Wg/Wnt signals through the seven-transmembrane receptor Frizzled (Fz) to inhibit phosphorylation of Armadillo (Arm)/β-catenin. Without activation of the Wg/Wnt signals, phosphorylation of Arm/β-catenin is maintained by glycogen synthase kinase-3β (GSK-3β). When Wg/Wnt is coupled to Fz, GSK-3β is inhibited by a large cytoplasmic complex, which includes Dishevelled and adenomatous polyposis coli (APC). This inhibition of GSK-3β allows unphosphorylated Arm/β-catenin to shuttle into the nucleus and affect the transcription of downstream target genes through the TCF/LEF transcription factor.

Cerberus, Wnt inhibitory factor (WIF), Frizzled-related proteins (FRPs) and Dickkopf (Dkk, which means 'fat head' in German) are all known antagonists of the Wnt pathway, but the mechanism by which Dkk inhibits Wnt has remained unknown. Previous work has shown that Cerberus, WIF and the FRPs all act by binding and sequestering Wnt, preventing the signal from interacting with its receptor. Mao *et al.* and Bafico *et al.* now show that Dkk does not bind to either Wnt or Fz.

As both groups had seen that Dkk is part of a large cellular complex, they identified the components of this complex that interact with Dkk. The two groups showed that LRP6 and LRP5 — which encode low-density lipoprotein-related co-receptors and act as positive regulators of the Wg/Wnt pathway — are specific, high-affinity receptors for the two *Xenopus laevis* Dkk homologues, Dkk1 and Dkk2. The domains necessary for this interaction were identified and are distinct from the regions of LRP6 that interact with either Wnt or Fz. Bafico *et al.* went on to show that overexpression of LRP6 markedly interferes with Dkk inhibition of Wnt signalling — if excess LRP6 is present, the concentration of Dkk needed to prevent Wnt signalling is increased 100-fold.

The Wg/Wnt pathway is vital during the development of many organisms including *Drosophila melanogaster* and *Xenopus*, and APC and β-catenin have been implicated in human cancer. So it is imperative to understand how antagonists of the Wg/Wnt pathway work. It seems that Dkk works by binding to the LRP6 and LRP5 co-receptors, which increase the interaction between Wnt and Fz and might also interact directly with the β-catenin degradation complex to inhibit Wnt signalling in an indirect manner. As this is the first inhibitor of the Wg/Wnt pathway found to act in this way, this work should expand our understanding of this increasingly important signalling pathway.

Sarah Greaves
Senior Editor, Nature Cell Biology

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PLANT MICROBIOLOGY

Quorum quenching

A bacterial quorum is not unlike the human variety — as soon as enough individuals are gathered together, decisions can be made. For bacteria, these decisions result from the production of signals that switch on genes involved in processes such as virulence. But a report by Lian-Hui Zhang and colleagues in *Nature* now shows that such decisions can be reversed by 'quenching' these quorum signals.

Bacterial quorum sensing, as it's called, is a response to increased population density that is often associated with a shift from a free-living to host-associated lifestyle. Individual bacteria produce quorum-sensing signals such as *N*-acyl homoserine lactones (AHLs) and, once the concentration of these signals reaches a certain threshold, the AHLs interact with transcription factors to activate gene expression. Different bacterial species may produce different AHLs, which vary in the length and substitution of the acyl chain, but maintain the same homoserine lactone moiety.

Last year, Zhang and colleagues showed that the *aiiA* (for 'autoinducer inactivation') gene from *Bacillus* sp. encodes a factor that can inactivate AHLs, suggesting that it might be possible to control bacterial infection by paralysing the quorum-sensing system. The authors have now further characterized AiiA by using it to digest several AHLs. In each case they found the molecular mass of the AHL to be increased by 18 after the enzymatic digestion, indicating the addition of a water molecule. This is consistent with hydrolysis of the ester bond of the homoserine lactone ring, leading the authors to conclude that AiiA is an AHL-lactonase.

The authors next investigated the effect of this enzyme on bacterial infection by introducing the *aiiA* gene into tobacco and potato plants. They then inoculated these transgenic plants with *Erwinia carotovora*, a bacterial pathogen that causes wilts and soft rots in crop plants. And the results were dramatic — there was a strong correlation between resistance to disease and the levels of the AHL-lactonase. This resistance also correlated with the population density of the *Erwinia*, such that high levels of the pathogen caused extensive tissue damage to controls, and even to some of the transgenic plants. Nonetheless, the transgenic plants were able to resolve the infection over time.

As Zhang and colleagues point out, their results show that enzymatic quenching of AHL quorum-sensing signals (an effect that they call 'quorum quenching') is a feasible approach for preventing bacterial infection. And, as quorum sensing is a common strategy adopted by many pathogens, this approach could be widely applicable.

Alison Mitchell

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