

sis of the receptor. Although they could not pinpoint the intracellular location of the cleavage event, an intense perinuclear accumulation of the DFrizzled2 extracellular domain is intriguing and raises the possibility that the cleavage and/or delivery of the intracellular fragment occurs at or near the nuclear membrane.

A correlation does not prove function, however, so the authors tested the requirement for receptor cleavage in Wingless signaling at the synapse. For multiple Wingless-mediated signaling events, DFrizzled2 activity is redundant with that of *Drosophila* Frizzled1 (10). However, synaptic maturation at the neuromuscular junction only requires DFrizzled2, and this allowed Mathew *et al.* to perform genetic studies and show that forms of DFrizzled2 that cannot be cleaved do not provide effective rescue of the DFrizzled2 mutant phenotype.

These observations are surprising and raise several questions. In the past few years, cleavage of the intracellular domain of some cell surface receptors (e.g. Notch) has emerged as a way of modulating their

activity (11, 12). In all known cases, this is mediated by the γ -secretase complex and usually involves cleavage within the transmembrane domain. The observations of Mathew *et al.* (5) uncover a previously unknown mechanism that invites a closer examination of the activity and mode of action of the Frizzled receptor family. A second question concerns the exact role of the cleaved fragment. Although its presence in the nucleus in transcriptionally active areas suggests a role in gene expression, this remains to be shown. Mathew *et al.* have shown that cleavage is necessary for DFrizzled2 function at the neuromuscular junction—that is, to promote synapse maturation. However, they did not show that the intracellular domain itself provides that function, because expression of a soluble version of this domain has no activity. Perhaps the cleaved receptor is recycled to the cell surface or to some intracellular compartment where it acts in a functionally altered manner, and the carboxyl-terminal fragment is merely a by-product of the process.

The observation that cleavage is trig-

gered by Wingless echoes the unsolved question of how interactions between particular Wnt proteins and specific Frizzled receptors can elicit different molecular and mechanistic responses. Given the versatility of Frizzled-Wnt interactions in controlling signaling events and biological processes, it is not surprising that at the synapse, a highly specialized structure, these receptors and ligands exert their functional potential with an unexpected molecular twist.

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10.1126/science.1121906

ATMOSPHERIC SCIENCE

Tiny Bubbles Tell All

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During the past 200 years, humans have caused a remarkable change in the levels of several atmospheric greenhouse gases. We know this from direct measurements that started in the latter half of the 20th century, but for earlier times we rely on tiny samples of the atmosphere trapped in polar ice. Coring the polar ice sheets provides access to these samples and allows us to place modern changes in the context of long-term natural cycles in greenhouse gases. Until recently, the longest of these ice core records (from Vostok Station in Antarctica) extended back 440,000 years (1). Now, reports by Siegenthaler *et al.* on page 1313 (2) and by Spahni *et al.* on page 1317 (3) extend our window into the past an additional 210,000 years.

The new ice core records come from the European Project for Ice Coring in Antarctica (EPICA) (see the figure). EPICA, an international collaboration of scientists, engineers, and drillers, made a major contribution to the study of past climates by recovering this deep ice core in East Antarctica where low snowfall rates

allow the accumulation of an extremely old section of ice (4). One of the new findings from this project concerns the nature of long-term glacial-interglacial climate cycles. Ice core scientists use the ratio of deuterium to hydrogen in ice as a proxy for temperature. Records from EPICA Dome C show a strong 100,000-year periodicity for the past 740,000 years (4). The existence of this cycle is well known from ocean sediments and other types of climate records. Its origin is enigmatic, because external climate forcing caused by changes in Earth's orbit is weak on this time scale. In the Dome C record the oldest three cycles are of lower amplitude than their later cousins. The reason for the shift from low- to high-amplitude cycles is not clear, but an obvious question concerns the behavior of the major greenhouse gases during the older time period (4).

Siegenthaler *et al.* (2) and Spahni *et al.* (3) address this issue with new records of atmospheric carbon dioxide, methane, and nitrous oxide, created through the collaborative efforts of two European research groups. They combine their work on Dome C with previous work on Vostok and other ice cores to create records of these gases covering the past 650,000 years. These new

records will no doubt become canonical figures in the global change literature, as did the Vostok records before them (1).

Two basic messages are apparent in this extended history of the atmosphere. First, even with this longer perspective, the modern atmosphere is still highly anomalous. At no time in the past 650,000 years is there evidence for levels of carbon dioxide or methane significantly higher than values just before the Industrial Revolution. Second, the covariation of carbon dioxide and methane with climate, strikingly evident in the Vostok record, follows essentially the same pattern in the earlier time period. The muted climate cycles (as indicated by the deuterium content of the ice) are accompanied by equally muted cycles of carbon dioxide and methane (see the figure). This relationship reinforces the view that the large-scale cycles in Antarctic temperature have global importance, and that climate and greenhouse gas cycles are intimately related.

For nitrous oxide, the picture is slightly less clear. The record is not complete, making it difficult to judge how or whether the amplitude of 100,000-year cycles changed with time, and anomalous levels of nitrous oxide appear to be related to high levels of dust in the ice. This had been observed before and was attributed to microbial activity in ice with high levels of terrigenous dust (5). Spahni *et al.* argue plausibly that the enrichment is significant only in very dusty ice, and use dust records to determine which samples they feel are reliable (3). This is probably the

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