Abstractions

FIRST AUTHOR

Warfarin has long been a household name thanks to its uses as a drug and in controlling rodent pests. Its protein target is less well known — the enzyme VKOR, which, in mammals, catalyses the generation of vitamin K hydroquinone. This is an important component in the vitamin K cycle and is required to sustain blood coagulation. Until now, no one had been able to determine exactly how mammalian VKOR worked because nobody had succeeded in purifying sufficient quantities for structural studies. Weikai Li at Harvard Medical School in Boston, Massachusetts, and his colleagues have now discovered a stable bacterial version of VKOR that has allowed them to examine the enzyme's crystal structure (see page 507). Li tells *Nature* more.

Why did you do this study?

We wanted to understand how mammalian VKOR works because its function has important medical implications. Warfarin is a commonly used anticoagulant drug that works by inhibiting VKOR, but it has a narrow therapeutic window. Too large a dose can cause lethal bleeding; too low and it isn't effective. Genetic variations exist in VKOR among patients, which affect the enzyme's sensitivity to warfarin, and that's one of the reasons it is hard to get the dose right.

What challenges did you face?

First we had to screen a number of bacterial VKOR variants to find one that would be appropriate for structural studies. Then we had to isolate the protein. For that, we had to find the right detergent: one that could dissolve the membrane surrounding the protein without denaturing the protein. The next step was obtaining pure and regularly ordered crystals that would yield the best diffraction. That's an essential and often rate-limiting step in structure determination.

Are your findings of value to human health?

Some people have mutations in VKOR that make it resistant to warfarin. By viewing the protein's structure, we can see the locations of mutated amino acids. A better understanding of how these amino acids interact with the drug may make it possible to devise a safer anticoagulant that's easier to dose than warfarin. Safe, appropriate dosage is crucial — a blood clot in the leg of someone who's received a subtherapeutic dose might travel to the lung and kill the person.

Are there any other implications?

A colleague of ours discovered that the bacterium that causes tuberculosis uses a protein homologous to VKOR. It's a separate study, but our work may help his group to design new antibiotics for tuberculosis. ■

MAKING THE PAPER

David Frank

Wealth of data cuts uncertainty in climate-warming predictions.

Human activities are largely to blame for the rise in atomspheric carbon dioxide that has seen global temperatures climb since the mid-twentieth century. But higher temperatures also cause more CO_2 to be released into the atmosphere through the natural processes of the carbon cycle. This feedback loop may play an important part in amplifying anthropogenic warming. However, determining the magnitude of such an effect has been a challenge.

"We know that anthropogenic CO_2 is having an effect on climate," says David Frank, a climatologist at the Swiss Federal Research Institute WSL in Birmensdorf. This is mainly because CO_2 traps heat from the Sun's rays, so the more we release into the atmosphere, the more heat is stored. But climate models have estimated that the feedback between the carbon cycle and climate could contribute anywhere between 0.1 °C and 1.5 °C per year on top of the rise in temperature due to direct anthropogenic emissions.

It has been difficult to precisely quantify the sensitivity of the carbon cycle to changes in temperature, partly, Frank says, because "during the past century the feedback relationship between temperature and CO_2 has been obscured by the massive amounts of CO_2 released by human activities. We therefore need to look at changes in temperature and CO_2 over a longer timescale, before the industrial revolution."

Other groups had already examined the relationship between temperature and CO_2 during pre-industrial times, explains Frank, but they typically based their calculations on a single reconstruction of temperature over time and a single CO_2 record. "It is as though you want to determine the average height of a population by measuring the height of one or two individuals," says Frank. Just as variations in individuals' heights could skew the average one way or the other, preferentially using data sets that indicate a small temperature variation and a large change in CO_2 would result in calculating a large feedback between the carbon cycle and temperature.

The solution that Frank and his colleagues came up with was to use every piece of data they could get their hands on. That meant combining data from nine large-scale temperature reconstructions and CO_2 records obtained from three Antarctic ice cores. After poring over "a heck of a lot of data", they were able to calculate more than 200,000 estimates of how CO_2 varied in response to temperature between 1050 and 1800. "These estimates take into account the uncertainties of reconstructions," explains Frank. "If the data were perfect, we might not need so many estimates."

From these estimates, the researchers were able to calculate probability distributions and then determine a median value for the magnitude of the carbon cycle's sensitivity to temperature. That value, 7.7 parts per million by volume of CO_2 per 1 °C, gives some idea of how much the ocean and terrestrial ecosystems will amplify anthropogenic actions by in the future (see page 527). "These values are similar to those obtained from climate models, although models with lower feedback might be slightly more accurate," says Frank. But he adds a caveat. "We don't know whether additional processes that have not been operating or significant in the past will have an important role in the future." ■

FROM THE BLOGOSPHERE

A recent literature search had Jennifer Rohn, a posdoc at University College London, seeing double. On her Nature Network blog, Mind the Gap, she describes how she turned up what seemed to be the exact same paper, with the same author list, published in two journals (go.nature.com/SDZ8Ja).

On closer inspection, Rohn finds that the two papers are identical. One is published in *Cell*, whereas the other features as a chapter in a meeting proceedings book. "How common is this sort of double publication? And how do people feel about it?" asks Rohn, opening up a lengthy discussion.

Those commenting speculate that the book chapter was an obligation filled with an easy, already-finished manuscript or that a junior author submitted the second version without the senior author's knowledge. One commenter wonders whether a duplicate set he found should be turned in as scientific misconduct. Meanwhile, on a related note, another person observes that publishing papers in different languages reaches more readers. Doubling up, it seems, is a grey area of scientific publication. ■

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