Title

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Quick guide:

Cobamides

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Cobamides? Never heard of them…

Perhaps you have heard of vitamin B_{12} – also called cobalamin (Figure 1A)? It's a very common dietary supplement and happens to be a cobamide, one of many that exist in nature.

What are cobamides and what do they do?

Cobamides are a group of organometallic cofactors that contain cobalt. Among the elements on Earth, metals are excellent enzymatic catalysts for otherwise challenging redox and radical-based reactions. Iron, magnesium and zinc are a few examples of metals commonly found in enzymes that are essential for life on Earth. Whereas some metals are directly bound by enzymes, others may be housed within an organic cofactor that an enzyme can then bind. Similar to how heme contains iron and chlorophyll contains magnesium, cobamides contain cobalt. By using cobamides as coenzymes, organisms are able to harness the catalytic potential of cobalt (Figure 1B).

Where do cobamides like B_{12} come from?

Although we are able to get most of the vitamins we need from plant-based foods, vitamin B_{12} is different. It's the only known essential human micronutrient made exclusively by prokaryotes. In fact, all cobamides – even industrially produced vitamin B_{12} used in supplements – were originally assembled in a bacterial or archaeal cell.

I've heard that elderly people are prone to B_{12} deficiency. Why is that?

Advanced age is a common risk factor, but there are many routes to B_{12} deficiency. A common cause in all age groups is insufficient B_{12} consumption. This most often affects people with diets lacking B_{12}-rich animal products like meat, fish, eggs, and dairy. Unlike animals, plants neither use nor store cobamides in their tissues, making plant-based foods generally inadequate sources of B_{12}.

Among people who regularly consume animal products, B_{12} deficiency can be caused by defective B_{12} absorption in the gastrointestinal tract. The first identified B_{12}-absorption disorder was the autoimmune disease known as pernicious anemia. A series of landmark

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studies in the 1920s showed that fatal progression of pernicious anemia could be stalled by feeding patients excessive amounts of raw liver. This eventually led to the identification of vitamin B_{12} as the active medicinal component of liver extract in 1948, sparking the development of the cobamide research field.

Do bacteria in fermented plant foods such as kimchi, injera, and kombucha make B_{12}?

Fermented plant-based foods are generally poor dietary sources of B_{12} mainly because there's simply not enough B_{12} produced by these fermentations. Also, bacteria can make many different cobamides, not just B_{12}. In fact, there's been some confusion in the past about the B_{12} content of foods because common assays used to measure B_{12} content do not distinguish B_{12} from other cobamides. For example, the dietary supplement spirulina, which is made of dried cyanobacteria, is popular among vegetarians in part because it was initially thought to contain a lot of B_{12}. Unfortunately, chemical analysis showed that the major cobamide in spirulina is actually pseudo-B_{12}, a cobamide that humans can't absorb. The search continues for alternative B_{12} sources in traditional fermented as well as engineered foods. A reliable plant-based food source of B_{12} would be beneficial, especially for populations with limited access to animal-based products.

What other cobamides are there?

The other cobamides are chemical analogs of B_{12}. The conserved cobamide structure consists of a cobalt ion chelated by an organic corrin ring, and a nucleotide loop extending from the corrin ring. The variable parts of a cobamide are known as the upper and lower axial ligands of the cobalt ion (Figure 1A). The combination of known upper and lower ligand variants suggests there are more than 30 naturally occurring cobamides!

Why are there so many cobamides?

Microbes make and use cobamides for a wide range of metabolic reactions. A convenient explanation for the chemical diversity is that each cobamide has a distinct metabolic role. However, it's not quite that simple. Microbes are typically somewhat flexible, such that several cobamides with different lower ligands can support their metabolism, but with varying efficiency. Thus, microbes appear to have ranked 'preferences' in cobamide usage, and the order of these preferences varies between species. Perhaps these quantitative differences in cobamide preference among microbes reflect an evolutionary game of balancing specialization with flexibility, while at the same time competing for prized cobamide resources in dynamic environments. Or perhaps limited availability of cellular metabolites drove the evolution of cobamide-dependent processes to make use of different lower ligands.

We already know so much about B_{12}. Why bother studying the other cobamides?

It’s true – we’ve learned quite a bit about B_{12} and its roles in human health and disease, but there is still a lot to learn about the importance of other cobamides in microbes. Consider that many bacteria use cobamides in processes that may help or harm us. Insights into how and why bacteria make so many cobamides could lead to useful applications for controlling these important microbial communities.

Controlling microbes with cobamides? How might that work?

About half of bacterial species that use cobamides can’t make their own and instead use what they find in the environment. This implies that cobamides are transferred between microbes (Figure 1C). This interaction between cobamide producers and users presents an opportunity to manipulate the composition of a community based on the cobamide ‘preferences’ of its members. Feeding specific cobamides to a microbial community of interest, such as the human gut microbiota, may enrich for growth of beneficial species over harmful ones (or potentially do the opposite). The major obstacle to this ambitious application is that the cobamide preferences of the vast majority of microbes remain unknown. Identifying the genetic basis of cobamide specificity is an ongoing effort by several labs.

What are some other open questions?

Cobamides have been studied for over 70 years, but there are still mysteries about what they do and how they function. Although a given microbial species may have specific cobamide preferences under defined laboratory conditions, it remains unclear how these preferences play out in natural environments where numerous microbial species coexist. New chemical and computational tools are opening up new avenues for cobamide research. For example, B_{12}-based probes are revealing novel facets of cobamide trafficking and new types of B_{12}-binding proteins. Also, novel functions and catalytic mechanisms of microbial B_{12}-dependent enzymes have been discovered in recent years. Some of these enzymes have been implicated in antibiotic production and gene regulation, yet the substrates and functions of others remain unknown, hinting at new cobamide-dependent processes waiting to be uncovered.

Where can I find out more?

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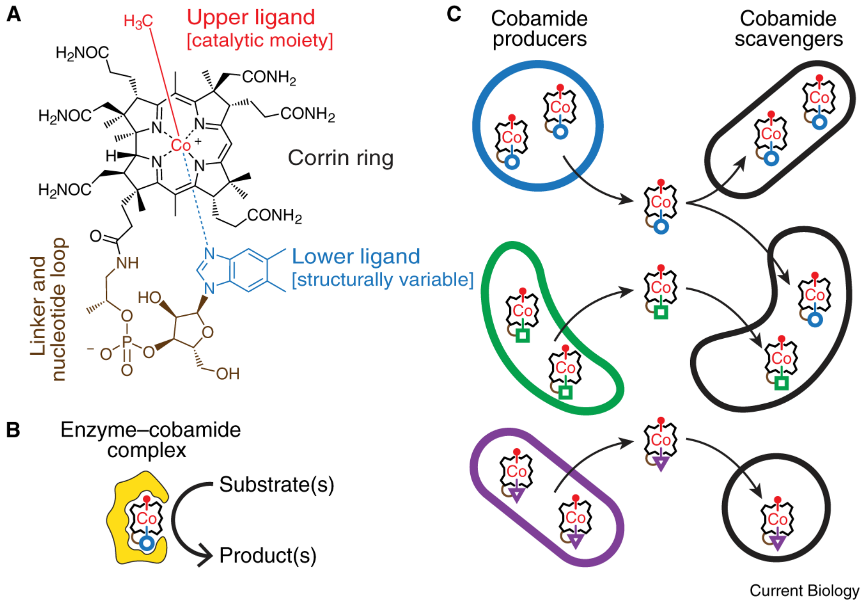

Figure 1. Cobamides – forms and functions.

(A) B_{12} is a cobamide essential for human health. (B) Cobamides function as coenzymes in numerous metabolic pathways within all domains of life. (C) Diverse cobamides are produced by bacteria and used by other members of a microbial community.