Carb synthesis sheds light on promising tuberculosis drug target

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A fundamental question about how sugar units are strung together into long carbohydrate chains has also pinpointed a promising way to target new medicines against tuberculosis.

Working with components of the tuberculosis bacterium, researchers from the University of Wisconsin-Madison identified an unusual process by which the pathogen builds an important structural carbohydrate. In addition to its implications for human health, the mechanism offers insight into a widespread but poorly understood basic biological function — controlling the length of carbohydrate polymers.

"Carbohydrate polymers are the most abundant organic molecules on the planet, and it's amazing that we don't know more about these are made," says Laura Kiessling, a professor of chemistry and biochemistry at UW-Madison. "There's not much known about how length is controlled in these carbohydrate polymers."

Kiessling is senior author, along with graduate students John May and Rebecca Splain and postdoctoral fellow Christine Brotschi, of a new study appearing in the online Early Edition of the Proceedings of the National Academy of Sciences the week of June 22.

Most carbohydrates exist as many sugar molecules linked into long chains, or polymers. The right number of sugars in the chain is vital for them to work properly, but different types of carbohydrate polymers range from a few dozen sugars in some bacterial molecules to tens of

thousands of sugar links in cellulose, a common plant material.

Despite its importance, it's not clear how carbohydrate length is determined, Kiessling says. Unlike some biological chains — such as DNA and proteins — that are built off a template that guides the length of the final product, carbohydrate-synthesizing enzymes work without templates.

"Nature has strategies to generate polymers of different lengths, but we know very little about those strategies," she says. "If you make something too short, it's probably not going to function in the role that you want, and if you make something too long, you're wasting energy that you need to use elsewhere."

The research team focused on an enzyme called GlfT2 that is responsible for building a critical carbohydrate component of the TB bacterial cell wall.

The researchers found that a small fatty component at the starting end binds to the enzyme and helps it track the length of the growing polymer. As the enzyme adds more and more sugar units to the opposite end, the chain becomes increasingly unwieldy.

"If the chain gets too long, it gets hard to hold on to both of the ends, so the chain falls off" the synthesizing enzyme, Kiessling says, forming a completed carbohydrate polymer.

The researchers believe that the enzymes responsible for building different types of carbohydrates exceed their comfort level at different points, leading to molecules of different prescribed lengths.

The current report is the first description of this "tethering" mechanism — named for the fatty lipid that tethers the start of the polymer to the

enzyme — in carbohydrate synthesis, Kiessling says, though it may prove to be common among other organisms as well.

In addition to providing insight into what may be a general mechanism for designing and building carbohydrates, the work gives insight into developing new therapeutics against TB. The GlfT2 enzyme is essential for bacterial survival and growth but has never yet been targeted by potential treatment methods. Knowing that the enzyme has two binding sites — one for each end of the growing carbohydrate — makes it an especially appealing candidate.

"Our mechanism provides a blueprint for strategies to block a new anti-mycobacterial target," Kiessling says.

New drug targets will be critical in the fight against tuberculosis, as drug-resistant strains are becoming increasingly widespread. The carbohydrate-synthesizing enzyme represents an untapped and promising resource for crippling even strains that are resistant to current drugs.

The prevalence of carbohydrate polymers in biological systems also means that understanding how their length is controlled has many possible applications, ranging from designing more potent and effective vaccines to facilitating the production of useful fuels from plant materials.

"It's a nice illustration of how basic research can lead to applications that are very practical," says Kiessling.

Source: University of Wisconsin-Madison (news : web)