From bugs to drugs

July 18 2019, by Dr Charvy Narain

Credit: AI-generated image (disclaimer)

A new study led by Prof Shoumo Bhattacharya has decoded the structure of unique proteins found in tick saliva and created new ones not found in nature, paving the way for a new generation of "Swiss-army knife' anti-inflammatory drugs, with customized extensions to block different inflammatory pathways.

Previous research by Prof Bhattacharya underlines that tick saliva can be

a pharmacological gold mine, potentially yielding many new drugs which could treat disorders ranging from cardiovascular diseases and stroke to arthritis. This previous work identified a group of tick saliva proteins called evasins, which bind to and neutralize chemokines, a group of chemicals key to causing inflammation in the body.

Now the researchers have worked out the structural trick that enables tick evasins to block a complex pathway that has multiple routes to the same response. What's more, they can now manipulate this structure to make new, custom-made proteins based on tick evasins.

But why ticks?

"Ticks have been around since before the time of dinosaurs, and they've have a few million years to evolve ways of biting and feeding off animals without triggering their inflammatory cascade," says Professor Bhattacharya. "If you're walking through a tick-infected field and get bitten by a tick, you're unlikely to even notice."

Once attached to an animal, ticks can feed for 8-10 days, successfully blocking pain, clotting and the body's normal inflammatory response to injury.

This inflammation is part of the body's standard immune response: when tissues are damaged by for example, an infection, they send out distress signals, in the form of the chemokine proteins. White blood cells response to these signals and appear at the scene of infection or injury, to clear up damaged tissues and fight any infection.

Going rogue

"This process is usually helpful, but sometimes, the white blood cells

basically lose the plot and cause further damage," says Professor Bhattacharya.

This runaway, damage-causing inflammation is a key player in many diseases, including the aftermath of a heart attack, myocarditis (where the heart muscle becomes inflamed, resulting in sudden cardiac death in otherwise healthy young adults), strokes, arthritis, psoriasis, tumor inflammation, and inflammatory bowel disease.

So researchers have been looking for ways to block inflammation, as a way to treat these diseases or at least reduce the severity of painful symptoms in patients.

This turns out to be a more difficult problem than it seems, because the inflammatory pathway has multiple, redundant pathways, and blocking just one or even several receptors has little effect.

Professor Bhattacharya says: "The chemokine pathway evolved as a way to fight infections and foreign pathogens, so it's evolved to be very hard to knock down.

"The complexity of the network is hard to communicate: there are 47 different chemokines, which bind to 19 different receptions, and there are over 24 different white blood cell types. There is not a single available drug that blocks the chemokine network."

Changing research focus

Professor Bhattacharya is the British Heart Foundation Professor of Cardiovascular Medication at the Radcliffe Department of Medicine—his main research interest lies in cardiovascular research, where rogue inflammation such as myocarditis was proving to be a vexing problem.

"But there are no effective anti-chemokine drugs in the clinic." Says Professor Bhattacharya. "What we did know is that blocking a single receptor or chemokine in the complex chemokine network has minimal effect."

The idea of the studying ticks came from a Google search highlighting the tick's abilities to evade the inflammatory response, something that the world's leading researchers haven't been able to recreate independently in the lab. Aided by the Radcliffe Department of Medicine pump priming awards, which aim to foster new ideas, Professor Bhattacharya repurposed his lab's skills to identify some of the 1,500-3,000 proteins found in a tick's saliva that would block chemokines.

The result of this work was the discovery of 40 chemokine binding proteins that could do what no other anti-chemokine drug can do: take down the entire chemokine pro-inflammatory network.

Studying the pharmacological goldmine in tick saliva is now the main focus for Prof Bhattacharya's lab, and his team have developed a new method for finding and isolating new tick proteins.

Dr. Angela Lee, the first author on the group's latest study, explains: "We synthesize the tick genes chemically and insert them into yeast cells to make a tick protein 'library' of sorts. The yeast cells now display tick peptides on their surface, and we then 'bait' them: we mix the yeast with a fluorescent chemokine, and the yeast cells that take the chemokine bait now glow. We can then pull out the glowing yeast, find out the DNA sequence of the new evasins, and grow large amounts of these new evasins in kidney cells in a petri-dish."

Using this method, the research team has cloned over 40 new tick evasin genes over the last two years, and found two distinct types of tick evasins

that block the two major different groups of chemokines.

Unique structure

But how does tick evasins bind so many different chemokines at once? This is the question that the group's latest study tackled, as it decodes the structure of the new tick evasins that bind to the CXC group of chemokines. Dr. Angela Lee says: "We found that the EVA3 evasin has a 'knotted' structure, with each loop of the knot creating a surface that can bind a different chemokine. This is how tick evasins can bind to so many different chemokines."

The team also went one step further, by transplanting the loops from one type of tick evasin into another type, to create a new hybrid protein with properties of both types. The hope is that these customized proteins could be used to treat a variety of inflammatory illness, from heart disease to arthritis to inflammatory bowel disease.

"We're still a very long way from getting drugs based on their tick proteins to patients," says Professor Bhattacharya, who is currently working with Oxford University Innovation to develop the research further, "But tick evasins have been 300 million years in the making, and we do hope to get drugs based on evasins into clinics quicker than that!"

More information: Angela W. Lee et al. A knottin scaffold directs the CXC-chemokine-binding specificity of tick evasins, *Journal of Biological Chemistry* (2019). DOI: 10.1074/jbc.RA119.008817

Provided by Oxford Science Blog