Could a 'leaky gut' be behind coeliac disease?

Autoimmunity is the catch-all description for conditions in which one's immune system attacks the body. According to traditional thinking, two things must occur for autoimmune diseases, which include conditions as diverse as multiple sclerosis, scleroderma, and type 1 diabetes, to develop.

The first necessary precondition is that patients are born with the genetic predisposition to develop immunity to self. Secondly, during a period in their lives, they must also have been exposed to an environmental antigen trigger that sets off a never-ending cycle of autoimmunity, driven by antigen mimicry. Recent evidence, however, supports the existence of a third leg of autoimmunity-that the barrier function of various tissues of autoimmune patients is impaired, especially the GI tract. This state of impaired barrier function involves the increased paracellular permeability of the intestine, otherwise known as "a leaky gut."

Barrier integrity

The founders of Alba Therabeutics Corp. believe they have identified the pathway and a key protein associated with paracellular permeability, as well as peptides that can up- or down-regulate barrier integrity. With that understanding, Alba is developing therapeutics for coeliac disease, type 1 diabetes and other autoimmune diseases, and is also harnessing the pathway as a vaccine adjuvant and drug delivery vehicle.

The paracellular space, or the space between cells, "used to be thought of as the equivalent of grout between tiles," explains Alba's CEO and cofounder, Blake Paterson. Nothing was supposed to get through, but substances sometimes did, presumably because of barrier injury or damage. Otherwise it was inert.

That was until the work of Alessio Fasano, Alba's second co-founder, and his colleagues, who identified a signaling pathway that regulated a reversible physiologic and transient opening and closing of the tight junctions of the paracellular space.

"The reality is that the paracellular space is a gate, not a wall or a fence," Paterson says. And if material gets through that space — even if it is only 1-5% of what normally travels through the cell — it could be associated with disease.

"What's different about the paracellular space is that what comes through has not been processed by the cell," he points out. "It has not been subjected to lysosomal digestion, nor has it been packaged for presentation to macrophages or lymphocytes."

Indeed, Paterson asserts, if Alba is correct, tight junctions "could be the dark horse responsible for a host of disease states, from acute injury all the way to chronic inflammatory or autoimmune states."

If the inappropriate paracellular permeability of physiological barriers is a third precondition of autoimmunity, "it is no longer an issue that, once triggered, a patient will inevitably suffer the ravages of autoimmunity. Rather," he goes on, "there is the possibility of an inmate factor serving as the driving force for the disease that can be blocked."

Zonulin uncovered

The key molecule in the signaling pathway regulating the opening and closing of tight junctions is zonulin, which Fasano discovered first in bacteria (the cholera organism uses the prokaryotic equivalent of zonulin to help it invade the sub-mucosal space), then later in eukaryotic tissue, while at the University of Maryland. Fasano also discovered small peptide agonists and antagonists of zonulin, giving him the empirical means to regulate the pathway.

By the time Paterson encountered Fasano, the researcher had begun to demonstrate the therapeutic utility of down-regulating intestinal permeability in coeliac disease.

Unlike other autoimmune conditions, the environmental trigger (the second precondition of autoimmunity) in coeliac disease has been identified: it is the presence of gluten in the diet. When gluten is removed, a significant percentage of coeliac disease patients go into remission. Classic small bowel histopathology returns to normal, as does intestinal permeability, and serological markers for the disease become negative.

Fasano has shown in ex vivo tissue taken from coeliac disease patients that exposure to gluten triggers zonulin release, which parallels, in both time and magnitude, an increase in flux across the tight junctions in the intestine, which he could then block with the zonulin peptide antagonist. Conversely, giving the zonulin peptide agonist increases the flux across the junction. Fasano has also shown in animal models that by opening the tight junctions with the agonist, that it could be used as vaccine adjuvant and as a delivery vehicle when co-administered with a drug.

Start up launched

Paterson first heard of zonulin and Fasano's work in late 2003, via a tech transfer posting on the Internet put out by the university, seeking licensees for drug delivery applications of the work. Both men felt the bigger opportunity lay in therapeutic applications, however—finding a way to block excessive permeability across various barriers, with sufficient time and magnitude to prevent the inappropriate presentation of antigen and thereby achieve disease-modifying potential for autoimmune and inflammatory conditions. With $2 million in seed capital raised by Paterson from friends the state of Maryland, and industry contacts in 2004 and early 2005, the duo formed Alba, which licensed therapeutic and drug delivery rights to Fasano's work, which by then included a 100-plus portfolio of issued patents and applications. Later, Alba added diagnostic rights to its IP.

The start-up decided to first test the zonulin peptide antagonist, AT-1001, in coeliac disease. That made sense from a safety perspective because in its normal resting state, the small bowel (where the majority of food absorption and the majority of immune surveillance occurs) is empty and sterile. "By the time food is digested and reaches the ileum, typically it has been chewed up and no longer has immunogenic potential," explains Paterson, who by then had also devised a coated formulation for the peptide to allow it to pass through the stomach. AT-1001 completed an initial Phase I trial in October 2005 and has been awarded fast track status by the US Food and Drug Administration.

Alba is also exploring the use of AT-1001 as therapy in other indications including IBD, IBS, asthma and type 1 diabetes. "It's known that 40-60% of type 1 diabetics have significant elevated intestinal permeability," says Paterson. And as in coeliac disease the trigger for its onset is thought to come through the gut, he points out, citing adaptive immunology work in the last three to four years that has tracked the locus of immunologic activity in type 1 diabetes from the mesenteric lymph nodes to the pancreas, where insulin-producing beta islet cells reside. Moreover, Alba had a leg up because Fasano had already used the BB/wor rat model for type 1 diabetes to demonstrate the link between tight junction regulation and autoimmunity.

In a set of controlled experiments in 2003 and 2004, he tested the effect of putting AT-1001 in BB/wor rats' drinking water. While 80-90% of the animals in the placebo group developed disease (they fell into diabetic coma), only 30% of those who got AT-1001 did. To show AT-1001's ability to treat disease, Paterson and Fasano then gave rats that had already developed autoimmunity the zonulin peptide antagonist: half recovered, and half of those got sick again when AT-1001 was subsequently removed.

Funding

To fund its rapidly expanding clinical operations, the start-up raised $30 million in a Series A round in August 2005. It was able to raise that hefty amount, says Paterson, based on its team, the network of resources the firm had put together, and importantly, "what we'd been able to do in a year with less than $2 million," he says – advancing two molecules (AT-1001 and the zonulin peptide agonist, AT-1002) that had been sitting on a shelf in an academic environment. Alba is also reigniting discussions with pharma companies on vaccine and drug delivery applications for AT-1002, which it had put on the back burner while it developed its therapeutic strategy. The firm has concluded one research collaboration that yielded positive results using AT-1002 as a drug delivery vehicle, according to Paterson.

The recent publication of new literature on the importance of tight junctions in inflammatory and immune diseases also puts Alba "in a sweet spot," Paterson points out. "The zonulin receptor appears to be ubiquitous, and if it proves to have clinical significance, the sky's the limit. Zonulin is the only pathway known to modulate the state of assembly of tight junctions in a reversible, nondestructive manner," he claims.

Before co-founding Alba, Blake Paterson was COO of Integrity Pharmaceutical Corp., a urology women's health company. Prior to that, he was executive director of the oncology acute care and inflammation product groups at Eli Lilly & Co. He also held positions at Parke-Davis Pharmceutical Research, where he was responsible for clinical research and medical, safety and regulatory affairs for the Latin America region. — MLR.