KINERET IL-1 PODCAST SERIES • PODCAST TRANSCRIPT

IL-1 biology and clinical features of NOMID

An expert discussion of IL-1 biology, its role in autoinflammatory disease, and the clinical features and management of NOMID and related disorders.

FEATURED SPEAKERS

01 HOST · PAEDIATRIC RHEUMATOLOGY
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ABBREVIATIONS USED IN THIS TRANSCRIPT

CAPS = cryopyrin-associated periodic syndromes; **CNS** = central nervous system; **CRP** = C-reactive protein; **FDA** = Food and Drug Administration; **IL-1** = interleukin-1; **IL-18** = interleukin-18; **JIA** = juvenile idiopathic arthritis; **NOMID** = neonatal-onset multisystem inflammatory disease; **RA** = rheumatoid arthritis; **SAA** = serum amyloid A; **UCL** = University College London.

TRANSCRIPT

IL-1 biology and clinical features of NOMID

NARRATOR

This is a promotional podcast series on autoinflammation and interleukin-1, sponsored and funded by Sobi. The views and experiences put forward in this podcast series are that of the speakers and do not necessarily reflect those of Sobi.

PROF. ATHIMALAIPET RAMANAN

Welcome to this podcast on the role of IL-1 in inflammation. My name is Ram. I'm a paediatric rheumatologist and professor of paediatric rheumatology at Bristol Royal Hospital for Children and University of Bristol. I'm joined today by my colleague, Professor Helen Lachman. As many of you may know, IL-1 is a key mediator of autoinflammatory disorders. And today, we'll be taking you through a journey about the discovery of this molecule, the mechanism of action, the laboratory and clinical features. Helen.

PROF. HELEN LACHMAN

Thank you, Ram. My name's Helen Lachman. I'm a professor of medicine at UCL, and I do my clinical practice at the Royal Free Hospital in London where I run a service treating adolescents and adults with autoinflammatory diseases. And I've been interested in these diseases and in the role of blocking IL-1 now for more than twenty years.

So, the discovery of interleukin-1 is a fascinating story and is really credited to Professor Charles Dinarello in the United States, who's now recognized as one of the founding fathers of cytokines. The history of fever and investigation of history of fevers in man is a fabulous story. Really dates back about three thousand years to when people became interested in the association between fevers and infection. But by 1943, doctors became more interested in the underlying mechanisms of fever, and particularly in what happened in patients who were febrile without evidence of infection. What about patients with autoimmune diseases who had very high fever but clearly weren't infected? And by the 1970s, Professor Dinarello discovered a class of molecules, which were initially referred to as leukocytic pyrogens. He purified these in 1974, and it was discovered that, in particular, there were two molecules that produced fever. And eventually these were given the names interleukin-1 alpha and 1 beta. IL-1 alpha and beta are now frequently referred to as the IL-1 or the IL-1 cytokines.

In 1977, Charles Dinarello published a paper from his team showing that picomolar, very small, quantities of interleukin-1 was sufficient to cause fever in a rabbit, thereby demonstrating that IL-1 was an extremely potent pyrogen and capable of triggering inflammation in tiny quantities. So this is a very potent proinflammatory cytokine, but what are the mechanisms by which this happens? So, looking further at the mechanisms by which IL-1 mediates inflammation, it's clear that IL-1 alpha and beta both bind to the same cell surface receptors. This is IL-1 receptor I and the IL-1 receptor accessory protein, and when these two receptors are brought together, this triggers an intracellular cascade of events that results in release of other proinflammatory cytokines, and these play pivotal roles in the inflammatory response.

If we start with interleukin-1 alpha, we know that the precursor lL-1 alpha is constitutively expressed in healthy cells and is biologically active even in this form. IL-1 alpha is released from dying cells, binds to the receptors, and triggers production of inflammatory mediators as cells die. This is the first step in sterile inflammation, which can occur in response to tissue injury of a variety of types. Consequently, IL-1 alpha is classified as an alarmin. It requires no buildup time for synthesis, and it functions as soon as it's released from the dying cell.

PROF. HELEN LACHMAN

In contrast, interleukin-1 beta is not available in healthy cells. It requires time to be produced before it can result in intracellular responses. It's only produced by a number of classes of cells, particularly neutrophils and macrophages, and it's reproduced in response to a number of triggers. Some of these are pathogen-associated triggers. Some of them are damage-associated triggers that are produced by the body itself. And the first step in the production of IL-1 is also the slowest, which is the transcription of the gene. The IL-1 beta that is produced after gene transcription is pro-IL-1 beta, and that is inactive, and it needs to be activated by cleavage. And the cleavage of pro-IL-1 beta to IL-1 beta is regulated by an assembly of molecules within the cytokine of specific cells, which is called the IL-1 inflammasome. And once this is activated, this produces active caspase-1, which cleaves pro-IL-1 beta to active IL-1 beta, which is then released from the cells in a regulated fashion. An activated IL-1 beta then triggers inflammation and plays a role both in triggering inflammation and in adaptive immunity.

These IL-1 alpha and beta act on the cells around them and produce a cascade of inflammation resulting in production of additional IL-1 and other inflammatory cytokines causing a positive autoinflammatory feedback loop. Question then becomes: can this loop be broken? And the answer is it can. And so the results of this have demonstrated that there are negative homeostatic mechanisms and, in particular, looking back at Professor Dinarello's research, an important member of the IL-1 family is important in downregulating this response, and this is the IL-1 receptor antagonist. This is a predominantly anti-inflammatory protein, which opposes the actions of IL-1 alpha and beta. And there has now been the availability of specific IL-1–targeting agents of a variety of types has shown in clinical practice in patients with disease that IL-1 is an important mediator of a variety of diseases in humans, in particular, autoinflammatory diseases, but also some autoimmune diseases.

PROF. ATHIMALAIPET RAMANAN

Thank you very much, Helen; that's a fascinating history of IL-1. I wonder, given that so much of what we do in autoimmune autoinflammatory disorders across the spectrum of conditions, which range from autoimmune to autoinflammatory with monoclonal antibodies, that Charles Dinarello's work, do you think at some point in time would be considered for a Nobel Prize given how pivotal some of these discoveries are in our understanding of the interaction between innate adaptive immune systems, between infection and non-infection driven, as you pointed out, with the pathogen-associated or the damage-associated molecular markers?

PROF. HELEN LACHMAN

I certainly think he's a real candidate, and it's, you know, it has translated into enormous human benefit and has also, his work has resulted in major increases in understanding of human disease and really the importance of innate immunity in general. It's also an example of how important it is to give time in science. These discoveries started from the 1970s, but just how applicable it was to humans in terms of treating disease and understanding specific diseases really didn't become apparent until thirty years later with the recognition of the role in the inflammasomopathies and recognition that CAPS was the first genetically defined disease that resulted in overproduction of interleukin-1.

PROF. ATHIMALAIPET RAMANAN

So, you've heard very well and clearly from Helen about the role of IL-1, the proinflammatory cytokine, and about the availability of specific IL-1–targeting agents. And autoinflammatory disorders, as has been mentioned, are predominantly mediated by the innate immune system, whereas the adaptive immune system is primarily involved in autoimmune diseases. So, an example of a primarily autoinflammatory disorder would be CAPS. And an example of an autoimmune disease or a predominantly autoimmune disease would be systemic lupus erythematosus.

PROF. ATHIMALAIPET RAMANAN

And over the years, people have characterized the spectrum of autoimmunity and autoinflammation in different formats such as response to IL-1 being an identifying feature, the absence of an autoantibody being an identifying feature. But it's important to remember autoinflammatory and autoimmune diseases are not necessarily to be seen as two ends of a spectrum and that there can be a lot of overlap. A host of conditions can sit in the middle with features of autoimmunity and features of autoinflammation. And some of these examples are what I highlighted, and the ones which sit in the middle may be conditions such as inflammatory bowel disease, some forms of rheumatoid arthritis. And examples of autoimmune diseases such as lupus may also, on occasions, benefit from therapies which are mediating the autoinflammatory cascade, as we realize increasingly with the interferon pathway. So, there is more overlap between autoimmunity and autoinflammation and it's important to not see them as two ends of a spectrum.

Let's look at the common clinical features of autoinflammatory diseases. Apart from being an IL-1–driven disease, most of them are characterized primarily by fever, but they may also involve the skin, particularly in conditions such as cryopyrin-associated periodic fever syndrome, and of course the musculoskeletal system in conditions such as the neonatal-onset multisystem inflammatory disease. And certain inflammatory sites are very specific for IL-1–mediated diseases, such as the serous membranes like the pleura and peritoneum, where you get pleuritis. The CNS and the conjunctiva can also be involved in conditions such as CAPS. And patients frequently complain of fatigue or malaise and poor sleep. Helen, in your practice in autoinflammatory diseases, what do you find are the key laboratory markers that help you?

PROF. HELEN LACHMAN

So, I think one has to say that in terms of laboratory markers that are easily available during acute autoinflammatory flares, the hepatic acute phase response is always elevated. So, you would always expect, during periods of symptomatic disease, to see elevation of C-reactive protein. And if it's available to you, the other hepatic acute phase response, serum amyloid A protein, is also elevated. Most of these patients will have elevation of ferritin, which is also a raised acute phase response, but this needs to be interpreted in a little bit of caution in patients with long-standing genetic disease, because there's probably some crosstalk with hepcidin, which is involved in iron absorption. And so, these patients may have an underlying iron deficiency, and so the ferritin may not be quite as high as you would expect. We also see a neutrophil in leukocytosis. There is, and we'll come onto this, interest in novel biomarkers. And there's a need for some novel biomarkers here, so there's considerable interest research-wide around the world in whether there will be some more specific biomarkers that can help us here.

Measuring interleukin-1 itself is probably not that helpful outside of the laboratory because it's very tightly buffered. It works in an autocrine fashion, so between cells talking to each other, with very little leaking out into the systemic circulation. So even in IL-1–driven diseases we don't actually see very high levels of IL-1. IL-18 may be a more stable marker that can be measured in the circulation. And there are other potential very useful biomarkers, particularly the S100 proteins.

One of the difficulties in measuring autoinflammatory disease that we have is it's very apparent when patients have acute disease and when they don't, but particularly in the acquired diseases, is in predicting in patients who are in a very good response to treatment when you can withdraw treatment. And if there could be a biomarker that could tell you in a patient who is doing extremely well on therapy, those patients who are still going to be dependent on treatment and those patients in whom patients could be withdrawn because they've actually gone into a true remission. That would be an immensely useful biomarker and there's a huge amount of research at the moment looking at whether there are going to be predictive biomarkers that will help in deciding who can safely have their treatment withdrawn.

PROF. ATHIMALAIPET RAMANAN

That's very interesting. Some of those biomarkers and laboratory markers you mentioned really capture my attention. I'm going to focus on a more easily available biomarker, which has been around for ages, the serum amyloid A. Is there value in doing the SAA during an acute episode or is it a greater value in doing it in between episodes to analyze the risk of amyloidosis?

PROF. HELEN LACHMAN

So, amyloidosis, AA amyloidosis can complicate any of these diseases. The risk of AA amyloidosis is related to how long you've had inflammation for and how bad the inflammation is. And sustained inflammation is necessary for the risk of AA amyloidosis, but it's clearly not sufficient because the vast majority of patients who've had chronic inflammation will never get it. The autoinflammatory diseases seem to have a uniquely high risk of AA amyloidosis. We think patients with inflammation in between attacks are at more risk because to some extent, the area under the curve is higher. So, it's really important to identify patients who have sustained inflammation when they are not complaining of symptoms.

One issue that we see, particularly in adults, is that they've often gone many years without being diagnosed. And to some extent, they have both hardened to their symptoms and given up. They haven't been given a diagnosis. They often haven't been validated in terms of being recognized as being genuinely very sick, and they have handled this by deciding that they are not going to complain. And this means that they will often come saying they feel fine with evidence of quite substantial subclinical inflammation, and these are the group who are really at risk. So, it is always worth checking to ensure that when patients tell you they are well, their information is genuinely suppressed. And if you do genuinely suppress their inflammation for a while, their symptoms disappear. They do, can come back to you and say, "I never knew. I didn't understand that other people, when they say they were well, felt like this. I didn't know that was your life experience." And that's a really lovely thing when you treat people because you give them back hours and hours of a day of feeling well that they never knew they were supposed to have. So, I think it is definitely worth doing more between attacks than with attacks.

I would say, in general, serum amyloid A is a lovely protein to be able to check. It is more sensitive than CRP. But you can do most of this with C-reactive protein, provided C-reactive protein is used right down to its lower levels of sensitivity and not cut off at 5 milligrams per litre or 10 milligrams per litre. And provided this recognition that the aim of treatment in these patients is to completely normalize C-reactive protein to the levels that you'd expect to see in age-matched healthy individuals. So, it's not so much the specific test you do, but the recognition that you are trying to treat people, and the aim of therapy is to get them down to healthy, normal values.

PROF. ATHIMALAIPET RAMANAN

That's very interesting to hear your views on SAA as well as on CRP, which is far more easily available. So, we've heard about the pivotal role of IL-1 as a proinflammatory cytokine. We know that IL-1 RA agents have now been approved, and the first one to be approved by the FDA was anakinra, which is known by its trade name, Kineret, in 2001. Anakinra is a recombinant form of IL-1 RA, which blocks both IL-1 alpha and IL-1 beta. It works to reduce inflammation by supplementing naturally occurring endogenous IL-1 RA. Helen, in your practice, how useful have you found anakinra in the management of autoinflammatory and autoimmune diseases?

PROF. HELEN LACHMAN

I think one has to say in autoinflammatory diseases, it transformed care. So, before the availability of IL-1–blocking drugs, for most of these patients, there was no effective treatment. The only treatments that worked were high-dose corticosteroids, at a dose of either a milligram per kilogram or half a milligram per kilogram, so essentially at extremely toxic doses that couldn't be maintained. And so either these patients came to us with severe corticosteroid damage or they've never been treated. And to some extent, the patients who had not been treated were in better states. But the availability of IL-1–blocking drugs and the recognition that they were useful from the early 2000s onwards has been completely transformative. And particularly for the diseases for which there was no previous treatment, and that is CAPS in this case, it has totally transformed patient outlooks. And since this is a dominant disease, when you get a family, you will get quite a large number of affected family members. And because this presents in childhood, it's not just the affected family members, it's the unaffected family members as well, because disease in childhood affects the whole family really severely.

PROF. HELEN LACHMAN

So, the case I'm going to describe is now about fifteen years ago, and this is a young man who was referred to me with a very tentative referral from a rheumatologist outside London saying, "I just wonder whether you'd see and consider. I'm sure it isn't, but could you think about whether this might be an autoinflammatory disease?" And this young man came and wasn't confident enough to come on his own, so he came with his sister because he really didn't feel well enough or capable of coming to an outpatient clinic in London. And he was in his mid-twenties, deaf, rash, which was a little bit urticarial in nature, anemic, diffuse joint pains without evidence of joint destruction, and a very sad history of really not completing school very well due to persistent fatigue, and persistently trying to hold down a job but endlessly being let go because he was ill all the time, and he kept being admitted to hospital with fevers. We're quite nonspecific. Did he have a bit of inflammatory bowel disease? Did he have a bit of arthritis? And when I saw him in clinic, he had clubbing. He had a rather urticarial-looking rash. He had red eyes, and there was a history that he'd had a couple of episodes of uveitis. And he had well-preserved speech and language skills, but he had bilateral hearing aids because he had gradually lost hearing with evidence of sensorineural hearing loss through late childhood. And I thought this was a very characteristic history of CAPS, of cryopyrin-associated periodic fever syndrome.

He didn't think either of his parents were affected, but his older sister who'd come with him was also clubbed. When I asked her about her history, she was being managed for rheumatoid arthritis but was seronegative. When we did genetic testing on both of them, they had a CAPS-defining mutation. They both had persistent inflammation. They neither of them really complained of fever. They both of them, when we did their quality of life at baseline, didn't report a quality of life that was that different from normal. And with our young man, most of the discussion since has been about moving him through employment, and now discussion about risks to his children and what he would like to do about fertility planning. So that's a really nice example of late diagnosis of CAPS with the implication for other family members when you pick up one member, and not just of really quite severe disease-associated morbidity, which these patients often internalize and blame themselves for, but also that just the treatment long term has been remarkably safe and well tolerated.

PROF. ATHIMALAIPET RAMANAN

It's so interesting hearing about your case. It reminds me of a similar patient that was sent to me for an opinion, labelled as systemic onset JIA, who actually had uveitis and urticarial rash, boggy synovitis, was at CAPS. And what's startling about these patients is the impact IL-1 has, and they probably all have a degree of CNS irritability, which leads to educational underperformance, constantly feeling irritable or miserable. That's a fascinating case. And this, I think, increasingly, one would hope we are seeing less of these patients presenting with late-onset CAPS and more often presenting early as the awareness of autoinflammatory diseases increases. And podcasts like these will certainly help in increasing that awareness.

So, to recap what we have covered today, you heard the fascinating story from Helen about the discovery of IL-1, the background from Charles Dinarello's work, and how over time we've developed a greater understanding about IL-1 and its role in autoinflammatory and autoimmune diseases, and about the role of anakinra and IL-1 RA treatment that blocks both IL-1 alpha and IL-1 beta. Over to you, Helen.

PROF. HELEN LACHMAN

So, thank you very much for listening to this first cast in a podcast series from Sobi on the role of IL-1 and IL-1–mediated diseases.

NARRATOR

Thank you to our speakers for providing their insights on the role of IL-1 in inflammation. Sobi is a biopharmaceutical company headquartered in Stockholm, Sweden. Sobi's main focus is on therapies in the fields of hematology and immunology and deliver treatments to patients in more than 70 countries all over the world.

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