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Specific contributions and regulation of inflammasomes in systemic-onset juvenile idiopathic arthritis: from bench to bedside

Project details

Research Leader	Professor Fabio Martinon, Department of biochemistry, University of Lausanne
Participating Institutes	Department of biochemistry, University of Lausanne (UNIL) Unit of pediatric rheumatology and immunology, Department of pediatrics, University Hospital of Lausanne (CHUV)
Relevant conditions	Systemic-onset juvenile Idiopathic Arthritis (SoJIA), also called Still's disease
Project duration	3 years
Total project cost	CHF 255'000 (CHF 85'000 per annum)

What are the aims of this research?

Systemic-onset juvenile idiopathic arthritis (SoJIA) is a serious form of childhood arthritis, which is painful and causes great suffering due to arthritis in joints accompanied by fever, tiredness, rash, loss of weight and appetite. It can have many complications, including diseases of the lymph nodes, liver and spleen, and inflammation of other tissues affecting lungs, heart, or other abdominal organs. It is estimated to affect 6 per 100'000 children in Switzerland. Up to 50% of patients develop chronic arthritis and many are severely limited in their daily activities, and suffer joint destruction, retarded growth, osteoporosis, and psychological illness. The disease is not well-understood and there is currently no cure.

SoJIA is believed to be an autoinflammatory disease caused by overactivation of innate immune cells, which causes inflammation that attacks the child's own body. Inflammation is a response to infection or stress. Recognising how and why inflammation occurs in autoinflammatory diseases such as SoJIA is an important step to understanding and treating such diseases. Innate immune system sensors, called inflammasomes, may be key to triggering inflammatory reactions, and this research examines their role and the regulation in a small group of children with SoJIA, with specific focus on the interleukin (IL-1) molecule which is known to be implicated in SoJIA and whose production is regulated by inflammasomes.

Blocking IL-1 production can suppress the disease symptoms in some, but not in all, children. This research will attempt to understand how inflammasomes affect IL-1 production: whether the varying effectiveness of therapy in different children can be explained biologically, and if so, how exactly. Finally, the results may provide insights that could be used to improve therapy for the affected children.

Why is this research important?

Our study aims to answer key biological and medical questions as to the specific role of inflammasomes in how SoJIA develops. The identification of inflammasome-dependent mechanisms that are currently unclear could lead to better treatments using available drugs or the development of new drugs that directly target inflammasome components. Furthermore, research to understand inflammasome activation and regulation in SoJIA may provide an important opportunity to study general inflammasome regulatory mechanisms and thus gain basic insights into other auto-inflammatory diseases. The study of inflammasome regulation in laboratory animals is less likely to produce relevant insights, because due to genetic differences between humans and mice inflammasome regulatory mechanisms are very different.

How will the findings benefit patients?

Understanding the inflammatory processes in the outbreak of SoJIA may be a step toward earlier diagnosis and better treatment of the disease. Furthermore, this research will help target patients at the CHUV in Lausanne, and hopefully later at other treatment centres, who will benefit from an early anti-IL-1 treatment. It might shed light on other treatment options for non-responders to this therapy, thus preventing SoJIA in those children and young adults, who may otherwise experience serious complications and long-term disability.