Course Title (Svenska Benämning)
Biology of Inflammation (Inflammationsbiologi)

Course Number (Kursnummer)
2388

Credit Points (Antal högskolepoäng)
1.5

Level (Nivå)
Research Level (Forskarnivå)

Course Aims
This course will provide students with a broad spectrum overview of the field of inflammation biology and present the different technologies and methods employed in this type of research. Specific aims include the following:

- Convey to students the concept and rationale behind inflammation biology-related research approaches and experimental design.
- Provide an overview of available experimental methods/models as well as resources available at the Karolinska Institutet.
- Explain the role of inflammation in the etiology of inflammatory-related diseases such as cardiovascular disease.
- Educate students on the current state of inflammation biology and potential future research directions to assist students in applying this information to their research.

Learning Outcome (Kursens lärandemål)
Following successful completion of the course, the student will acquire a basic level of knowledge in the biology of inflammation and its role in inflammatory-related disease processes. In addition, students will be updated on recent findings within these fields. Specifically, students will be able to:

- Reflect on the utility of inflammation-related research in terms of hypothesis generation and experimental design.
- Relate to principle the appropriate applications of different experimental approaches and theory to questions of disease etiology.
- Theorize on the future development of inflammation-related research approaches and its role in observed pathologies, as well as motivate the answer.

Contents of the Course (Kursens innehåll)
This course will be focused on the following research areas:

1) To determine why chronic inflammation sometimes, but not always, results in increased atherosclerosis and leads to myocardial infarction or stroke (cardiovascular disease).

2) To identify novel therapy targets and investigate the effects of targeted therapies against chronic inflammatory diseases and cardiovascular diseases

Taken together, these two approaches will allow us to both understand the etiology and pathogenesis of chronic inflammatory diseases and cardiovascular disease and provide a basis for improved prevention and therapy for chronic inflammatory diseases and inflammatory cardiovascular disease, two major challenges to health in the population.

The development of cardiovascular disease (CVD) is dependent both on metabolic and inflammatory events and it is the most common cause of premature death in many chronic inflammatory diseases (CID). In spite of this, our understanding of the chronic inflammatory mechanisms that contribute to CVD is limited. CERIC will address this problem in a novel way, utilizing resources and opportunities already at hand in experimental and clinical research to form a world-leading research environment, where it will be possible to study the molecular pathogenesis of CID and CVD in well-defined clinical materials and animal models. The course will cover a number of diverse topics through its seminar series that includes key areas involved in the pathology of inflammation.

Atherosclerosis is an inflammatory disease that is associated with systemic immune responses and signs of inflammation. Its lesions are filled with immune cells that can orchestrate and effect inflammatory responses. In fact, the first lesions of atherosclerosis consist of macrophages and T cells. Unstable plaques are particularly rich in activated immune cells, suggesting that they may initiate plaque activation. Experiments in gene-targeted mice have provided mechanistic evidence that immune mechanisms are involved in atherosclerosis. During recent years, we have seen a rapid increase in understanding of the mechanisms that govern the recruitment, differentiation and activation of immune cells in atherosclerosis. Experimental research has identified several candidate antigens and there is encouraging data suggesting that immune modulation as well as immunization can reduce the progression of the disease.

This course will specifically address these areas:

- chronic inflammation and atherosclerosis – mechanistic studies in experimental models
- inflammatory signalling in atherosclerosis and chronic inflammation – exploration of the transcriptome and proteome in human disease
- immune activation and autoimmune cross-reactions in chronic inflammatory disorders
- shared effector molecules in the molecular pathogenesis of chronic inflammatory diseases

The role of B lymphocytes in chronic inflammatory diseases will be addressed with the aim of understanding pathogenic processes and identifying targets for therapeutic intervention. We will focus on Sjögren's syndrome and congenital heart block using basic molecular studies, analysis in experimental models and clinical investigations.

This course will specifically address these areas:

- dissect genetic contribution to the autoimmune associated congential heart block

- delineate the role of TRIM21/Ro52 in regulation of interferon responses and development of chronic autoimmune disease

Recent evidence suggests that a previously unnoticed cytomegalovirus (CMV) infection can be detected in tissue specimens from patients with many inflammatory diseases such as cardiovascular diseases, autoimmune diseases as well as certain cancers. CMV infects and is carried by 70-100% of the world's population. For many years, CMV was not considered to be a major human pathogen, since the virus only caused rare cases of CMV inclusion disease in neonates. CMV is an important pathogen in immunosuppressed patients such as transplant patients and AIDS patients. CMV disease in these groups of patients has also high-lightened the role of the virus in the development of other inflammatory diseases.

This course will specifically address these areas:

- To further understand how CMV is involved in the development of inflammatory diseases.

- To further understand the role of CMV as a link between rheumatic diseases and cardiovascular diseases.

Arachidonic acid is the precursor of a broad spectrum of bioactive lipids in plants and animals. In mammals, the most well known classes are the prostaglandins, thromboxanes, leukotrienes and lipoxins which all have powerful and diverse biological activities related to a multitude of physiological as well as pathological conditions. We will focus on a family of lipid mediators called the leukotrienes (LT) involved in a number of inflammatory and allergic diseases, in particular asthma, rheumatoid arthritis, and arteriosclerosis.
Based on research on metabolites and proteins in the arachidonic cascade, a number of new drugs against inflammation, allergy, asthma and glaucoma have been developed and new pharmacological principles continuously evolve from this research area.

This course will specifically address these areas:

- Studies on the role of eicosanoids in atherosclerosis and CVD

- Elucidation of lipid and peptide mediator synergies in the innate immune response

- Impact of CMV infection on cellular eicosanoid synthesis and actions

- Effects of anti-inflammatory, anti-rheumatic drugs on the eicosanoid cascade

Antimicrobial peptides are effector molecules in innate immunity and can be considered endogenous antibiotics. The peptides are present in several blood cells with the highest concentration in neutrophils, the first cells recruited to a site of infection. The peptides represent key defense-components at epithelial surfaces, the barrier between the external environment and the interior milieu in humans. It has been found that some pathogens are able to turn off the expression of the endogenous antimicrobial peptides, resulting in serious infections. Interestingly, the short-chain fatty acid butyrate can counteract down-regulation as shown in experimental shigellosis.

This course will specifically address this area:

- The role of antimicrobial peptides and more specific LL-37 in chronic inflammatory diseases.

There are a range of factors involved in cardiovascular disease and it is important to identify and functionally characterise novel genes, genetic variants and pathways that confer susceptibility to coronary artery disease (CAD) and aneurysm formation. The tools to attain these goals comprise a combination of large-scale genome-wide association studies (GWAS), quantitative trait locus (QTL) mapping in humans and rodent models and gene expression profiling in rodent and human target tissues for the gene discovery phase, whereas the functional characterisation of candidate genes is performed in vitro as well as in vivo in model systems and in carefully phenotyped human subjects.

This course will specifically address these areas:

- To identify and functionally characterize susceptibility genes for cardiovascular disease, with particular emphasis placed on defining which allelic variants in immunoregulatory genes affect risk.

- To clarify which immunoregulatory pathways control atherosclerosis, plaque instability and clinical events such as myocardial infarction.

- To establish an animal model of both rheumatoid arthritis (RA) and atherosclerosis and to explore genes known to affect arthritis and/or atherosclerosis in the arthritis/atherosclerosis model.

- To identify common mechanisms for chronic inflammatory disorders by comparing genome wide scans of human cohorts suffering from either CAD, RA or multiple sclerosis.

In order to obtain basic biological knowledge explaining the development of autoimmune diseases such as rheumatoid arthritis and multiple sclerosis experimental animal models are often used. The ultimate goal is then to identify prognostic markers and to establish new therapies for these diseases.

This course will specifically address these areas:

- to develop an animal models and genetic platform for studies of pathogenic mechaisms in chronic inflammatory diseases

- to investigate in depth the genetic contorl of oxiudation pathways controlling autoimmunity and inflammation

- to validate new preventive and therapeutic possibilities for the future prevention and treatrment of chronic inflammatory diseases

Psoriasis is a common, hereditary and clinically highly heterogenous disease where the genetic background in combination with environmental triggers determine disease phenotype, severity and likely response to treatment. The ultimate cause for psoriasis is still unknown.

Using a Stockholm cohort of individuals diagnosed within maximum 12 months of disease onset, we study disease triggers, phenotype/genotype correlation, clinical course, comorbidities and response to treatment. Healthy individuals matched for sex and age serve as control. Even though skin is the main target organ, psoriasis is today considered as a systemic disease with significant co-morbidities such as arthritis and cardiovascular disease. Our cohort with carefully phenotyped patients coupled with an extensive biobank provide serves as our main research tool. Another line of research is the role for the human antimicrobial cathelicidin peptide LL-37 in chronic inflammation and as a driver for autoimmunity..

This course will specifically address these areas:

- Immunobiology of chronic inflammation
- Psoriasis , the metabolic syndrome and cardiovascular co-morbidity
- Common genes between psoriasis, MS and atherosclerosis ?
- The role of LL-37 in chronic inflammation and autoimmunity

Since MS is caused by inflammation, which can be controlled, the disease should in principle be curable or at least be possible to prevent to a large extent. Some of the currently available therapies, and those emerging, are in fact able to dampen the relapse rates up to 70 %. However, they broadly interfere with the immune system, which is needed in the defence against infections, and may be risky at a long term perspective. Therefore, the primary goal in a long term perspective is to achieve a more detailed knowledge on the exact modes and mechanisms in which the immune system is allowed to attack the nervous system in order to develop much more precise therapeutic interventions. In addition to the immune system, target-related factors may be important, both regarding local expression of molecules interacting with the immune system and factors relating to the susceptibility of the CNS to inflammatory damage.

Both environmental factors and gene variants contribute to the cause of MS. The genes involved are likely to be many, probably in the order of a hundred and therefore may differ between different individuals with MS. Nevertheless, exact knowledge of these risk genes may disclose critically regulated bottlenecks in disease pathogenesis. As for other autoimmune diseases this has been a working hypothesis for decades, but it is not until now, with recent technological and intellectual developments, that this can be properly studied. Classical hypothesis driven research focuses on single molecules. It carries the risk that years of work are spent on a mechanism of no relevance for disease. An alternative approach, which we have successfully used since many years, is to identify natural gene variants affecting disease course and susceptibility in rat models to pin point those molecular pathways which are central in disease pathogenesis. Once identified, these can then be dissected with classical techniques. In addition, association of human orthologues with disease can be studied in large case-control materials.

This course will specifically address these areas:

- Fine dissection of polymorphic genes regulating rat models of MS and inflammatory neurodegeneration after nerve trauma using advanced intercross lines (AIL), a

heterogeneous stock (HS) and recombinant congenic mapping under the assumption that interspecies conserved mechanism may be of relevance for human neuroinflammatory disease.

- By comparative genetics, study if the same gene, or genes in the same pathway, are of relevance in human disease.

- Functionally dissect these pathways in rodents, and also study potential therapeutic intervention.

- Study potential gene-environment interactions in a large ongoing case-control study.

Type of Teaching (Arbetsformer)
Research seminars and a written assignment.

Examination
Satisfactory completion of the course will be assessed by written examination consisting of a research report on an aspect of inflammation biology. The learning outcomes of the course have to be taken into account in this report. The exact subject of the report may be chosen by the student, but must be approved by the course organizer. The final report must be 3 A4 pages or less (12 point font, 2.54 cm margins) including references and must be turned in within 2 weeks of course completion in order to receive course credit (there is no minimum length). The report should make use of the journal articles and concepts discussed during the course, which are expected to generate ideas for the reports. In the event of an unsatisfactory report, as determined by the course organizer, the student will be given one additional week to re-write and resubmit the report.

Course Reading Material (Kurslitteratur)
On-line resources will be employed throughout the course.

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Lars Klareskog
Tomas Olsson
Anders Hamsten

Additional guest lecturers and keynote speakers will be included in the final course schedule.