Doctoral Thesis

HLA-DRB1 genes and effector mechanisms of inflammatory synovitis and rheumatoid joint distruction

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HLA-DRB1 GENES AND EFFECTOR MECHANISMS OF INFLAMMATORY SYNOVITIS AND RHEUMATOID JOINT DISTRUCTION

A dissertation submitted to the
SWISS FEDERAL INSTITUTE OF TECHNOLOGY ZURICH
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presented by
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Summary

The data presented in this study cover a broad range of areas of interest for further understanding the role of immunogenetics in RA and the immunopharmacology of therapeutic interventions with anti-TNF therapies.

1. Cytokines and cytokine inhibitors in RA

The data on cytokines, immunochemical markers and soluble factors from patients with rheumatoid arthritis confirm the dominant role of TNFα in inflammatory synovitis and structural joint damage.

The analysis of serum samples collected from RA patients during a clinical trial before and after administration of an anti-TNF-therapy (sTNF R55-IgG) revealed important information on the mode of action of anti-TNF therapies and indirectly, on the effect of TNF in up-regulating the effector mechanisms involved in RA. Systemic and synovial trapping of TNFα results in significant effects on clinical indices of inflammatory synovitis and laboratory parameters (CRP and ESR). Down-regulation of adhesion molecules ICAM-1, VCAM-1 and ELAM-1 results in a marked inhibition of migration of immune cells. A decrease of synovial cytokine expression of metalloproteinases results in a normalization of circulating pro MMP-1 and pro MMP-3 levels.

2. Immunogenetics in RA

Population genetics

Three different types of RA patients were analyzed for an association between disease parameters and HLA-DRB1 patterns:

- In a cross-sectional study "MUNICH study" 266 unselected patients were typed for HLA-DRB1 and analyzed for an association between HLA-DRB1 -defined sub-populations and radiographic status, disease activity and various soluble factors.
- A population presenting with early rheumatoid arthritis "HANNOVER study" was typed for HLA-DRB1 for future analysis between clinical features and outcome.
- A population of RA patient with erosive disease at study entry reflecting a poor prognosis was analyzed for the role of HLA-DRB1 genes in long-term disease
progression assessed by clinical and laboratory parameters and by radiographic changes over 6-10 years "RATINGEN study".

Patients recruited for studies soon after a preliminary diagnosis of RA were less frequently typed for alleles indicating a poor diagnosis. "HANNOVER study", whereas inclusion criteria such as the presence of erosive disease select more frequently patients with a double gene dose.

HLA-DRB1 genes and disease progression in RA:
Long-term assessment "RATINGEN study" of clinical, laboratory and radiographic disease progression in RA patients undergoing aggressive therapy did not show a significant role for genetic markers if patients were seropositive, but this patients had a significant poorer prognosis than seronegative patients. An important new finding of this study was the observation, that seronegative patients bearing a double dose are predisposed to an aggressive disease course and poor radiographic outcome.

3. Immunogenetics, immunochemical markers and molecular mechanisms of synovitis and structural joint damage

The physiological regulation of net cytokine is directed by the balance of pro-inflammatory cytokine and their inhibitors. The results of this study "MUNICH study" indicate that circulating levels of cytokine Inhibitors, which reflect their synovial expression, are significantly associated with the immunogenetic profile. Patients bearing none of the disease-linked HLA-DRB1 alleles have significantly higher circulating inhibitor levels which may enable them to a more efficient control of an increased release of pro-inflammatory cytokines. This phenomenon is also reflected by differences in the cytokine-mediated up-regulation of adhesion molecules and metalloproteinases. An important role within genetic contribution seems to be played by rheumatoid factors, so significant differences in some data were only due to seropositive or seronegative patients.

The data presented in this study contribute to a better understanding of the role of immunogenetics in RA and suggest evidence for a genetic control of the cytokine-cytokine inhibitor homeostasis pro-inflammatory activity in up-regulating effector molecules of synovitis and rheumatoid joint destruction.
4. Automation of HLA-typing

A robotic workstation was used to automate liquid handling in HLA-typing. Although RCR is a delicate method, reproducible results were obtained. No cross-contamination could be detected in over 700 amplification reactions.
Zusammenfassung


1. Zytokine und Zytokin-Inhibitoren

Die Daten über Zytokine, immunochemische Marker und lösliche Faktoren von Patienten mit Rheumatoider Arthritis (RA) bestätigen die dominante Rolle für Synovitis und Gelenkszerstörung.


2. Immungenetik der chronischen Polyarthritis

Populationsgenetik

In drei unterschiedlichen Populationen von RA-Patienten wurde die Beziehung zwischen Krankheitsparametern und HLA-DRB1 untersucht.

- In einer Querschnitts-Studie "MUNICH study" wurden bei 266 Patienten die HLA-DRB1 bestimmt. Die Ergebnisse wurden auf Unterschiede innerhalb der durch HLA-DRB1 Gene definierten Untergruppen und dem Krankheitszustand bzw. verschiedenen löslichen Faktoren untersucht.
• In einer Population mit früher Arthritis "HANNOVER study" wurden die HLA-DRB1 bestimmt, um klinische Daten zum Verlauf der Erkrankung mit dem HLA-DRB1 Muster korrelieren zu können.

• In einer Langzeitstudie "RATINGEN study" über 6-10 Jahre an RA-Patienten mit nachgewiesenen Erosionen beim Studienbeginn, aber schlechter Prognose, wurden die HLA-DRB1 Gentypen bestimmt auf Beziehung zu Klinik- und Laborparametern, sowie zu Röntgenbefunden untersucht.

Patienten, mit früher RA "HANNOVER study", hatten weniger häufig Allele-Kombination für die eine schlechte Prognose diskutiert wird. Hingegen zeigte die "RATINGEN study", in welcher eine erosive Form der Erkrankung Voraussetzung für die Rekrutierung war, eine deutlich erhöhte Anzahl von Patienten mit einer "double gene dose".

**HLA-DRB1 Gene und der Erkrankungsverlauf in RA**


**3. Immungenetik, immunochemische Marker und molekulare Mechanismen der Synovitis und der Gelenkzerstörung**

Die physiologische Regulation des Zytokin-Netzwerks wird durch ein Gleichgewicht von entzündungsfördernden Zytokinen und deren Inhibitoren kontrolliert. Die Daten dieser Studie "MUNICH study" zeigt, dass die zirkulierende Konzentration von Zytokin-Inhibitoren, welche die synovialen Verhältnisse widerspiegeln, eine signifikante Beziehung zum genetischen Profil aufweisen. Patienten ohne Arthritis-assoziierte-HLA-DRB1 Allele haben signifikant höhere Inhibitorkonzentrationen (sTNFR und sIL-1Ra) und können so die entzündungsfördernden Zytokine effizienter kontrollieren. Dieses
Phänomen zeigt sich auch bei der zytokin-induzierten Aktivierung von Adhäsionsmolekülen und Metalloproteinasen.

Die Daten, die in dieser Dissertation präsentiert werden, erweitern das Verständnis der Immungenetik bei RA. Sie unterstützen die These einer genetischen Kontrolle der Zytokin-Zytokininhibitor-Homöostase, der entzündungsfördernden Aktivität durch eine Up-Regulierung von Effektormolekülen der Synovitis und einer arthritisbedingten Gelenkszerstörung.

3 Automation der HLA-Bestimmungen