Karolinska Institutet

Institutionen för Medicin, Enheten för Reumatologi

MOLECULAR MECHANISMS IN IDIOPATHIC INFLAMMATORY MYOPATHIES

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i föreläsningssalen CMM, L8:00

Fredagen den 10 Oktober 2014, kl 9.00

Av

Mei Zong, MD

Huvudhandledare:
Professor Ingrid E. Lundberg
Karolinska Institutet
Institutionen för Medicin, Solna
Enheten för Reumatologi

Bihandledare:
Professor Helena Erlandsson Harris
Karolinska Institutet
Institutionen för Medicin, Solna
Enheten för Reumatologi

Professor Vivianne Malmström
Karolinska Institutet
Institutionen för Medicin, Solna
Enheten för Reumatologi

Extern Mentor:
Professor Agneta Nordenskjöld
Karolinska Institutet
Institutionen för Kvinnors och Barns Hälsa

Fakultetsopponent:
Associate Professor Patrizia Rovere-Querini
University Vita-Salute San Raffaele
Clinical Immunology Unit
Milan, Italy

Examination Board:
Docent Inger Gjertsson
Göteborgs Universitet, Sahlgrenska Akademin
Institutionen för Medicin
Avdelningen för Reumatologi och
Inflammationsforskning

Professor Anna Krook
Karolinska Institutet
Institutionen för Fysiologi och Farmakologi

Docent Christopher Sjöwall
Linköpings Universitet
Institutionen för Klinisk och Experimentell
Medicin , Enheten för Reumatologi

ABSTRACT

Background: Myositis is a group of rare autoimmune diseases. Muscle weakness and fatigue are the dominant symptoms and inflammation with T cells and macrophages is a characteristic finding in muscle tissue. Currently high-dose and long-term glucocorticoids is still the most important treatment but with limited efficacy and worrisome side effects. Therefore, investigations regarding inflammatory mediators and their roles in myositis pathogenesis are important in order to develop new therapies.

Methods: In order to investigate the roles of different inflammatory mediators in patients with myositis, biological samples were investigated from clinically well-characterized patients in different phases of disease. Several techniques were employed: immunohistochemical staining on muscle tissue and cultured skeletal muscle cells; flow cytometry, ELISA and chemiluminescence immunoassay on blood samples. Hypotheses regarding molecular mechanisms for muscle weakness and fatigue were tested in animal models, where we mainly used enzymatically dissociated muscle fibers and mechanically dissected muscle fibers to measure the force and calcium release from the sarcoplasmic reticulum under various defined molecular conditions.

Results: Based on previous observations on IL-1 expression in muscle tissue we first tested the role of IL-1 by using IL-1 blockade, anakinra, for 12 months in patients with refractory myositis. Eight of 15 patients had a clinical response which correlated to some response in biomarkers in blood, but muscle tissue inflammation persisted. Therefore, we searched for a new immune modulating target and found IL-15 to be expressed in muscle tissue of patients with myositis, and higher IL-15 expression was associated with more muscle dysfunction. Another approach was to test for the role of inflammatory molecules in early phases of muscle inflammation. In this context the extra nuclear presence of the alarmin high-mobility group box 1 (HMGB1) in the muscle fibers of patients with myositis without detectable inflammatory infiltrates is of interest. By *in vitro* experiments we showed that HMGB1 can influence muscle function by accelerating muscle fatigue and inducing MHC-class I expression via TLR4. Another receptor for HMGB1, TLR2, was also found in muscle tissue of patients with myositis and our animal study demonstrated that by knocking out TLR2 the skeletal muscle fibers became more muscle fatigue resistant.

Conclusion: Collectively, the investigations in my thesis suggest that inflammatory mediators play important roles in the pathogenesis of myositis and different molecules may contribute in different phases of disease. Hereby, HMGB1 might induce muscle dysfunction at an early stage of the disease via TLR4 (or/and TLR2). IL-15 could be involved in developing muscle dysfunction via maintaining T cell homeostasis in the muscles. IL-1 may be important in a subset of patients by driving the adaptive immune system. However, more studies are needed for a comprehensive understanding of their roles in order to develop new therapies.