Abstract ID: 93182

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Area of Research: Immunology, microbiome research and respiratory diseases

PhD Programme: PhD Immune Modulation in Respiratory Diseases (RESPImmun)

Semester: 5

The role of the molecular circadian clock in Asthma

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Asthma is a chronic inflammatory lung disease with a strong circadian signature. Nocturnal worsening of asthma is detected in 75% of all patients. At 4 a.m. most severe asthma attacks occur and the highest number of eosinophils, one of the main effector cells in asthma, is observed in the sputum. The molecular circadian clock produces oscillating expression patterns to time biological processes such as leukocyte trafficking. As disturbances in the circadian system can promote inflammatory diseases, this project aims to investigate the impact of the molecular circadian clock in asthma and clarify if exogenously applied ligands may represent a novel treatment approach in the future.

A comparison of the expression level of circadian nuclear receptors in leukocytes from asthmatic and healthy donors revealed significant differences of the expression level. Similar differences were observed by mimicking an inflammatory environment using sera from asthmatic patients or inflammatory mediators. The inverse ROR agonist SR1001 reduces the shape and migratory response, while decreasing respiratory burst and degranulation of human peripheral eosinophils. SR1001 treatment also affects nuclear circadian receptor expression and polarization of macrophages. Systemically applied SR1001 shows anti-inflammatory properties in vivo. Importantly, the treatment had no effect on rhythmic biological behaviour of the mice although the circadian clock is targeted.

We observed that circadian nuclear receptors are differentially expressed in leukocytes from asthmatic patients. Targeting the ROR receptor has an impact on the expression of nuclear circadian receptors and supresses effector cell functions of eosinophils, neutrophils and macrophages. Further SR1001 shows anti-inflammatory properties in vivo reducing the migratory responsiveness. Thus, exogenously applied inverse ROR agonists may represent a novel pharmacological approach for the treatment of allergic inflammation and asthma.