



Samenvatting proefschrift T. Yadati

'Small molecules, big consequences: novel therapeutic approaches for treating chronic inflammatory diseases'

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Obesity has become a global epidemic due to increase in sedentary lifestyle and calorie intake. In addition to increased BMI, obese patients display a persistent, low-grade inflammatory response known as "metabolic inflammation." This metabolic inflammation is linked to several diseases, including heart diseases, non-alcoholic fatty liver disease (NAFLD), type 2 diabetes as well as inflammatory bowel disease (IBD). The focus of this thesis is to understand the mechanism underlying these metabolic inflammatory processes with a goal to identify novel and safe therapeutic approaches.

One of the main mechanisms responsible for this metabolic inflammatory response is the disturbed cholesterol metabolism in macrophages, which are immune cells that kill and clear pathogens. Hence in thesis we focused on finding novel ways to improve cholesterol metabolism in macrophages and thereby reduce inflammation.

Previous research in our group identified a key role for lysosomes of hepatic macrophages in regulating the inflammatory response. Cathepsin D (CTSD) is a protease responsible for protein degradation in lysosomes. During inflammation, CTSD is released outside of the lysosomes and such CTSD levels and activity have been linked with metabolic disorders. We tested the role of lysosomal and extracellular CTSD fractions in NAFLD by using specific small-molecule inhibitors. Specific inhibition of extracellular CTSD activity led to reduced lipid levels and inflammatory responses in experimental mouse models of NAFLD. Therefore, extracellular cathepsin D might be a potential and safe therapeutic target.

In addition, we tested the potential of a cholesterol mobilizing agent, 2-hydroxypropyl- β -cyclodextrin (CD) in modulating metabolic inflammation. Besides reducing cholesterol, CD showed a dose and time-dependent effect on inflammation and hence should be used with caution in clinic. In addition to the above-mentioned pharmacological approaches, this thesis

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also discussed the importance of non-pharmacological stress-reduction strategies in controlling inflammation which can have a great effect in improving quality of life in these patients.

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