

The inflamed liver

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Valorisation

Valorisation

Obesity is a major risk factor for the development of NAFLD and CVD, while NAFLD itself is also associated with enhanced CVD risk¹⁻³. The work described in this thesis provides knowledge about the complex interplay between obesity, NAFLD and CVD. This is of great relevance considering the detrimental impact of these diseases on quality of life and all-cause mortality and the great economic burden on society due to the high costs of current therapies to treat liver disease and CVD^{4,5}.

The obtained results from the first part of this thesis indicate that both endogenous formation of AGEs and dietary intake of AGEs contribute to hepatic AGE accumulation. These AGEs might cause liver inflammation and contribute to low-grade inflammation. Hepatic inflammation and chronic low-grade inflammation are major factors in the progression of NAFLD toward irreversible liver damage and are associated with CVD^{3,6}. Therefore, prevention of inflammation could be of great benefit to people at risk for developing severe liver disease or atherosclerosis. Our results imply that both endogenous formation and dietary intake of AGEs are targets for intervention to combat inflammation. As previously described, there are several compounds capable of reducing endogenous AGE formation including the vitamin B6 analogue pyridoxamine. This compound can trap α -dicarbonyl compounds; major precursors in the formation of AGEs^{7,8}. In mice, pyridoxamine has already shown beneficial effects on AT inflammation and insulin sensitivity⁹. A study with pyridoxamine is under active clinical investigation in obese individuals with insulin sensitivity and microvascular function as primary outcomes. In this study, markers for liver injury will be assessed. If successful in reducing liver damage, pyridoxamine could be a safe supplementation for people at risk of cardiometabolic disease. Medical doctors and pharmaceutical companies will be informed about the outcomes of the pyridoxamine trial.

Results described in this thesis showed that dietary AGEs contribute to the overall level of circulating and hepatic AGEs. Therefore, reduction of dietary AGEs by changing dietary habits is an option to reduce the accumulation of AGEs throughout the body. Vlassara et al. have previously performed dietary

intervention studies focused on a reduction in AGE consumption and observed reduced oxidative stress and inflammation¹⁰. Current ongoing clinical studies aim to determine if a diet low in AGEs has beneficial effects on liver disease, insulin sensitivity and CVD. These studies will give insight into the importance of striving for a low AGE diet. At this moment, it will be highly challenging to actually reduce AGE levels in the diet of the general population, as it would require cooperation of food producers and a large-scale campaign to inform the public. Healthy eating is already stimulated via many channels: the internet, books, YouTube videos, cooking channels, etc. When the ongoing trials prove that low levels of dietary AGEs are beneficial, more awareness about the benefits of a low AGE diet should be created.

In the second part of this thesis, detrimental effects of ATMs on systemic inflammation and liver disease are described. Inhibition of the detrimental effects of ATMs could be a viable option for therapy to prevent the progression of NAFLD in obese individuals. The ATMs secrete factors (CXCLs, CSFs, S100A8/9) that recruit immune cells from the bone marrow contributing to hepatic inflammation. These soluble factors are present in the circulation, which makes them targetable by blocking antibodies. As such, blocking antibodies to inhibit cytokine, *e.g.* CXCL14, function could be developed, as previously shown in both experimental models and even humans¹¹. Another option to prevent cytokine function is the inhibition of its receptor. This has previously been shown to be a viable option for liver disease with the CCR2/CCR5 antagonist, Cenicriviroc¹². Although it has been recently demonstrated in a major clinical trial that the cytokine IL-1 β can be blocked in humans and that this can have beneficial effects on cardiovascular outcome, this therapy was non-specific and compromised the immune system resulting in increased infections and infection-related death¹³. Therefore, the blocking of cytokines that have more specific functions, such as CXCL14, will provide a more specific and thus safer approach.

Another interesting approach could be the modulation of specific ATMs, *i.e.* CD11c⁺ ATMs, to suppress their proinflammatory functions, such as the production of cytokines that recruit immune cells. In this thesis, we have described an association between classical monocytes and CD11c⁺ ATMs revealing their possible origin. Moreover, we determined that it are these specific CD11c⁺ ATMs that contribute to systemic inflammation and NAFLD

progression. However, more knowledge is required about the development, maintenance and modulation of macrophages in general to be able to modulate specific macrophage subsets in tissues. Fortunately, the so-called macrophage niches are currently the subject of intense research efforts. The macrophage niches are a relatively new concept which postulates that tissue macrophages, *e.g.* the ATMs, are dependent on environmental cues for their development, maintenance and tissue-specific functions¹⁴. These cues are thought to be derived from the stromal cells surrounding the macrophages within tissues. These stromal cells proposedly provide a 3D anchoring scaffold for the macrophages and nurture them by cell-cell contact and production of cytokines and metabolites^{14, 15}. This interaction between macrophages and stromal cells needs to be further investigated, but potentially consists of many targetable proteins. Affecting these proteins could allow suppression of specific macrophages, such as the proinflammatory CD11c⁺ macrophages, in the AT. This would mitigate one of the main limitations of current immunotherapy, namely specificity.

Besides targeting the ATMs and the factors they produce, the knowledge obtained about the release of cytokines from ATMs could be crucial for biomarker development. A panel of cytokines (CXCLs, CSFs and S100 proteins) could be measured in people at risk of cardiometabolic disease. Elevated levels of these markers could suggest an inflammatory state in the AT making the development and presence of advanced NAFLD more likely. Currently, the gold standard to diagnose NASH is still an invasive liver biopsy, which still has several limitations. If a combination of cytokine levels could give an indication of the presence of NASH, it would be a major advancement in the diagnosis of NAFLD. Of course, this needs to be tested and validated in large studies wherein sensitivity and specificity of these markers needs to be determined. The biomedical industry is very interested in developing a non-invasive method to diagnose NASH. If successful, the use of such a biomarker panel could be rapidly widespread.

It is clear that many years of additional research are required to translate the described research, as presented in this thesis, into therapy and/or biomarkers. By publishing many of the findings of this fundamental research, an important step towards valorisation has been made.

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