Bridging the gaps of microRNAs in obesity

Valorization

Societal impact

Obesity remains an insidious condition that raises the risk of morbidity from hypertension, dyslipidemia, type 2 diabetes, coronary heart disease, stroke, gallbladder disease, osteoarthritis, sleep apnea, endometrial, breast, prostate and colon cancer and embodies a major health burden (**Chapter 1**).[1] In addition to the comorbidities primarily mentioned in this thesis (**Chapter 1**), an important association has been reported between obesity and mental illness. Obese individuals further suffer from weight related social (and self-) stigma and discrimination with substantial contributions to psychological distress.[2] Obesity and psychiatric illness are often comorbid to one another and could be mediated by medical issues such as decreased mobility and chronic pain negatively impacting quality of life.[3] The ongoing increase in obesity has contributed to a dramatic shift in the prevalence of non-communicable diseases which contribute to 71% of all deaths globally.[4, 5] Of major concern is the tenfold increase in childhood and adolescent obesity over the past four decades.[6] This rise potentiates a generation to suffer from reduced quality of life, serious comorbidities and higher mortality at an earlier age with increased health care expenditures as compared to their parents.[7] Ultimately in light of the timing at which this thesis is written, which coincided with a global pandemic, it is inevitable to mention the societal consequences of this vulnerable population. The outbreak caused by the novel coronavirus that orchestrates severe acute respiratory syndrome (SARS-Co V-2) disease (COVID-19) was linked to severe and fatal outcomes with requirement of invasive mechanical ventilation especially in severe obesity.[8, 9] In young people with severe obesity the disease caused by SARS Co V2 could progress to destructive alveolitis with respiratory failure and death.[10, 11] These observations imposed an even higher burden on the very large part of the obese population globally. All this despite the fact that obesity is a preventable condition which further underlines the need for novel treatment paradigms, curtailing its progression. In this thesis tools to improve the detection of metabolic alterations in obesity and definitions for novel treatment paradigms in light of microRNAs were discussed.

Scientific Innovation and implementation

The etiology of obesity is complex and multifold, and involves interactions between genetics epigenetics and environmental factors in conjunction with social, behavioral, cultural physiological and metabolic factors.[1] Current preventive measures are inefficient as the rise in obesity has remained unabated and the trends described above are of major concern. The novelty of the research presented in this thesis provides interference at two different levels of obesity management. The first project aids at the diagnostic level, and benefits from the utility of a non-invasive stable marker present in the circulation that is specific to metabolic alterations and obesity (**Chapter 2**). The uniqueness of non-coding RNA as blood-based markers, is that it differs from conventional biomarkers that are mostly protein-based, could precede serious metabolic conditions, has a high stability in plasma, is resistant to storage handling, easily accessible and showed specific signatures

in different types of diseases (**Chapter 2**). Therefore, circulating microRNAs are attractive diagnostic tools and in the research presented in chapter 2 we corroborate its diagnostic potential which could contribute to monitor disease progression more accurately. However, before reaching its full diagnostic potential more research directed at the reproducibility and implementation as a diagnostic tool is needed.

Chapter 3 and **Chapter 4** were more focused on understanding epigenetic induction and treatment of obesity by microRNAs. In the past non-coding RNA were referred to as "noise", whereas now key regulatory functions have been unveiled with biological consequences. To date effective obesity treatment finds its basis in behavioral therapy with lifestyle interventions on one side of the spectrum and bariatric surgery on the other side of the spectrum which is directed at severe morbid obesity.[12, 13] Besides this there is an emerging field of available pharmaceuticals and antidiabetic medication with varying efficacy in weight reduction. Examples of such pharmaceuticals include, phentermine, orlistat, lorcarsin, phentermine combined with topiramate and naltrexone.[12, 13] However, there are still many challenges as these drugs are often contraindicated in patients with comorbid heart disease or mental illness as well as the fact that several side effects were reported involving gastrointestinal disorders with increased risks for valvular disease.[9] As both human and mouse models of obesity have specific non-coding RNA signatures in an organ-restricted manner, selective modulation of non-coding RNA expression is capable of providing remarkable therapeutic benefits in rodents (Chapter 3 and Chapter 4). The findings reported in this thesis strengthen the idea that microRNAs could serve as novel candidates for obesity therapeutics. The studies presented in this thesis are limited to the pre-clinical phase that should primarily be extended by in vivo studies addressing efficacy, toxicity and pharmacokinetics, and involve larger animals prior to advancing towards the clinical phase. As great success has been achieved in the treatment of hepatitis C using a hepatocyte targeted N-acetyl galactosamine conjugated oligonucleotide that antagonizes miR-122 in a phase 1B-double-blind randomized controlled trial, this development pioneers in the field of microRNA-based therapeutics.[14] To date several pharmaceutical and biotech companies have launched miRNA projects in their development pipeline, addressing both miRNA-based therapeutics and miRNA-based diagnostics.[15] Although the development and commercialization of new diagnostic and therapeutic tools is a long process, tremendous efforts are being made to bring these microRNAs from bench to bedside.[15] In addition the studies presented in this thesis contributed to these efforts by setting the first steps in the direction of bridging the gaps between fundamental processes in particular microRNA modulation and its prospective clinical purpose for obesity.

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