The Glasgow-Maastricht foot model

CHAPTER 8

Valorization

Cardiovascular diseases (CVDs) are the number one cause of hospitalization and death worldwide. Different CVDs include aneurysms, angina, arrhythmias, stroke, coronary artery disease (or CHD), myocardial infarction, valve problems (stenosis, regurgitation), hypertension, pulmonary heart disease, cardiomyopathy, and congestive heart failure. According to the most recent health statistics of the World Health Organization (WHO), an estimated number of 17.3 million people died from CVDs in 2008 of which 6.2 million were due to stroke and 7.3 million were due to coronary artery disease. More than 80% of the deaths occur in low- and middle-income countries, affection women and men in equal proportion.[*] In Europe, CVDs account for over 4 million deaths each year, with coronary heart disease (CHD) and stroke being the main forms. Almost half (47%) of all deaths are from CVD (52% of deaths in women and 42% of deaths in men). Just under half of all deaths from CVD in both men and women are from CHD, with stroke accounting for nearly a third of deaths in women and a quarter of deaths in men.[**]

While current pharmacological treatment strategies (e.g. β-blockers and ACE-inhibitors) have shown effectiveness in prolonging survival of heart failure patients, the prognosis of affected individuals remains poor and new therapeutic approaches for treatment of this devastating disease are still necessary. Besides the devastating effects on the quality of life of those patients (social burden), life-long treatment is expensive and increases the economic burden on society that comes with high healthcare costs.

Many risk factors are associated with CVD. Obesity[1], plasma triglyceride level[2], physical inactivity[3], elevated serum cholesterol level[4], cigarette smoking[5], hypertension[6], diabetes and glucose intolerance[7] are all primary risk factors for CVD. Metabolic syndrome is a cluster of metabolic conditions that can lead to CVD, including hypertension, abnormal cholesterol, insulin resistance, and obesity. Total blood volume and cardiac output correlate positively and proportionately with the degree of excess body weight, because of the high metabolic activity of excessive fat. The increased filling pressure and volume in obese patients often leads to development left ventricular eccentric hypertrophy and chamber dilation.[8] Body mass index in obese patients was also reported to correlate with other structural abnormalities such as left ventricular mass and wall thickness, and concentric remodeling.[9] Although some studies reported evidence of eccentric LV hypertrophy in obese patients[8,10,11], other studies of obese subjects found a predominance of concentric hypertrophy[12,13].

In this thesis we describe specific non-coding RNA species, long non-coding RNAs (lncRNAs) and microRNAs (miRs) that are involved in cardiac disease. The focus on RNA biology opens new avenues to improve our understanding of inter-cellular and inter-organic communication, increases our repertoire of available clinically useful biomarkers and innovative new medication for relevant human medical conditions.

The scientific results published in this thesis are particularly interesting for fellow researchers and pharmaceutical companies, since there is still a dire need for pharmaceutical treatment approaches. Here we identified miRs that are specifically involved in eccentric hypertrophy. The majority of current research on miRs in HF focuses on concentric hypertrophy and heart failure and it is still not clear what triggers the heart to activate pathways leading to eccentric remodeling. Further investigation of our described candidates can lead to identification of specific target molecules causing eccentric remodeling, and targeting these molecules could provide better-tailored therapy for patients. In this case our miRs would be used as tools to identify the mRNA targets that exert the effects.

Valorization of this kind of research can be the translation into patents, spin-off companies and licenses. When a therapeutic target is identified, the next step is to design a chemical or biological molecule that can target it. Efficacy, drug metabolism, pharmacokinetics and safety all have to be addressed in the pre-clinical phase. Drug metabolism and pharmacokinetics will be addressed further during clinical trial phases. Plenty of tests have to be completed before a therapeutic molecule can enter the clinical trial phases. For example, metabolism and clearance are tested by assessing stability in hepatocytes, human cytochrome P (CYP) isoforms involved and reactive intermediate formation. CYPs are the major enzymes involved in drug metabolism, accounting for about 75% of the total metabolism.[14] Regarding tissue distribution, exposure in efficacy in target tissue and major organs should be assessed, and plasma protein binding. To use our candidate miRs for therapeutic purposes, the hurdle that one miR can target dozens of mRNAs throughout the body has to be overcome. One way of circumventing targeting healthy organs is making the delivery of the miR modulator tissue-specific. Other important aspects to be addressed are human pharmacokinetics prediction and human dose prediction. Toxicology includes target assessment (physiological function, potential side effects, tissue distribution, cross-species comparison), genetic toxicity screening, and toleration studies.[***] All these and other issues have to be addressed before a drug can

proceed into phase I trials. It is evident that it still will take some time before those miRs are used as therapeutical targets in the clinic. This thesis aimed to provide a solid starting point for what miRs to pursue in the quest for molecular therapeutics for eccentric cardiac remodeling. Furthermore, we discussed the therapeutic potential of antisense oligonucleotides against miRs (Chapter 3) and briefly touched the subject of using lncRNAs as potential therapeutic targets (Chapter 7).

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