Adipose tissue-derived microRNAs as therapeutic targets in obesity-related atrial fibrillation

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Background
Atrial Fibrillation (AF) is the most common arrhythmia affecting 3% of the adult population, with major socioeconomic implications (Kirchhof et al., 2017). Obesity, is one of the strongest predictors of AF in both primary and secondary care (Nalliah et al., 2016). The links between obesity and AF however, are unclear, although it is now accepted that adipose tissue-derived products may have direct effects on myocardial biology, leading to arrhythmogenesis (Haemers et al., 2017). We have previously shown that myocardial oxidative stress, a major substrate predisposing to AF (Kim et al., 2008) (Tousoulis et al., 2009) is regulated by continuous interactions with adipose tissue, via paracrine (i.e. via the epicardial adipose tissue or EAT) and endocrine (e.g., via signalling originated by other fat depots like subcutaneous (ScAT) or thoracic (ThAT) adipose tissue) signals (Antonopoulos et al., 2016). The nature of the signals mediating the effects of “dysfunctional” adipose tissue on myocardial redox state and AF in humans are unclear.

Evidence suggests that microRNAs, small non-coding RNAs known to regulate biological processes by inhibition or degradation of specific messenger RNAs (Bartel, 2004), are highly expressed in the human adipose tissue (Icli and Feinberg, 2017). In a recent pilot screening of 356 miRNA expressed in human epicardial adipose tissue (EAT) obtained from patients undergoing cardiac surgery (from the Oxford Heart Vessels and Fat (ox-HVF) cohort), we have identified a subgroup that is also secreted by adipose tissue in exosomes and found that their expression/secretion from EAT correlates with myocardial redox state in 200 patients from the cohort.

Hypothesis
Obesity contributes to the myocardial substrate that promotes AF by increasing the expression and release of microRNAs from EAT and remote adipose tissue depots such as ScAT and ThAT. These microRNA networks may be targeted pharmacologically, preventing the cardiac consequences of obesity and metabolic syndrome.

Aims
Aim1: To identify microRNAs released from distinct human adipose tissue depots that are dysregulated in obesity and examine their effect on the atrial nitroso-redox balance and other signalling pathways (e.g., inflammation, fibrotic remodelling) subtending the new onset and maintenance of AF.
Aim 2: Validate the ability of the microRNA(s) identified in aim 1 to modify the biological substrate for the development of AF, using primary cardiomyocytes and cell lines.

Aim 3: Evaluate the value of the selected microRNA(s) measured in plasma and in different adipose tissue depots in predicting clinical endpoints.

Description of work
Aim 1: In a screening of 356 microRNAs, we have identified 6 that are expressed and released from human EAT and that are correlated with the myocardial redox state (i.e., atrial superoxide generation by NADPH oxidases, uncoupled NOS or mitochondrial oxidases). We propose to quantify the expression and release of the same microRNAs in ScAT and ThAT as well as their plasma levels in 200 patients undergoing cardiac surgery in the ox-HVF cohort, and compare them in patients with or without obesity, insulin resistance (HOMA-IR) or diabetes. Then we will evaluate whether these microRNAs predict the development of paroxysmal AF (identified in 33% of the ox-HVF participants during the post-operative period). We also propose to investigate the expression of key genes in the myocardium of these patients that are predicted to be targeted by these microRNAs that might be relevant to atrial fibrillation. A bioinformatics analysis will allow us to narrow down to a small group of microRNAs, that will be validated in aim 2.

Aim 2: Validate the ability of selected microRNA(s) in aim 1 to causally modify the biological substrate for the development of AF in primary cardiomyocytes and cell lines. By using microRNA mimics, inhibitors and target site blockers, we will explore the mechanisms by which these microRNAs modify the cellular mechanisms of PAF.

Aim 3: Validation of the target microRNAs against clinically relevant endpoints. The final microRNAs identified in aim 1 and validated in aim 2, will be quantified in adipose tissue and its secretome (EAT, ThAT and ScAT) as well as in the plasma of 1500 patients in the oxHVF cohort, and will be linked with incident of AF but also with other secondary outcomes like stroke, TIA and non-fatal MI and cardiovascular death during a follow up period of up to 10 years. Their interactions with obesity, insulin resistance and diabetes will also be evaluated.

The final goal of the project is to use unique resources available in the Division of Cardiovascular Medicine to identify a pool of adipose tissue-derived microRNAs that may explain the epidemiological link between obesity and AF and explore their downstream signalling with the aim of uncovering new druggable targets.

References


**Supervisor’s recent relevant publications**


