1. Introduction

1.1. Background

In this post-genomic era, the continuous advancement of high-throughput platforms has resulted in a surge of new biological data. Integration of the different omics data−namely genomics, epigenomics, transcriptomics, proteomics, metabolomics, and microbiomics−has been done to overcome the limitations of each data type (Hasin, Seldin, & Lusis, 2017). This multi-omics approach has been applied in elucidating complex biological processes tied to regulatory functions in the human body, as well as in various disease states, including cancers and cardiovascular diseases (CVDs) (Arneson et al., 2017). Intrinsic biological connections exist between the multi-omics environment, and epigenetics plays an integral role in regulating its dynamics (Shu, Arneson, & Yang, in press).

The epigenetic mechanisms shaping the epigenome consists of modifications affecting genomic sequences, yet recent studies have found that those modifications also exist at co- and post-transcriptional level; resulting in the blooming field of epitranscriptomics (Helm & Motorin, 2017). Such modifications include the process now called RNA editing, where RNA molecules undergo site-specific alterations independent of 5' capping, splicing, and polyadenylation–resulting in diversified gene products (Gott & Emeson, 2000). RNA editing affects both coding and non-coding regions, possibly causing changes in amino acid production in the former, as well as regulatory functions in the latter (Nishikura, 2016).

Adenine to Inosine (A-to-I) RNA editing has been established as the most common epigenetic mechanism affecting RNA sequences (Zinshteyn & Nishikura, 2009). The phenomenon is regulated by a family of enzymes called adenosine deaminases acting on RNA (ADARs), which transforms adenosine into inosine. The mechanism varies between species, cell types, as well as environmental conditions around the individual (Garrett & Rosenthal, 2012; Liu et al., 2016; Picardi et al., 2015; M. H. Tan et al., 2017; Yablonovitch et al., 2017). Studies about the mechanism have mainly revolved around the

development and diseases of the brain, as well as different types of cancers (Hwang et al., 2016; Xu, Wang, & Liang, 2018).

1.2. Objective

For over a decade, CVDs remain as the top cause of deaths worldwide, with ischemic heart disease (IHD)−frequently caused by coronary artery disease (CAD)−as well as stroke being the leading causes (WHO, 2017). The breadth of epitranscriptomics has been barely explored in the cardiovascular system, hence there is very little known about it. A-to-I RNA editing in human heart disease remains unexplored, despite its potential importance (Uchida & Jones, 2018). It is essential for researchers to understand the fundamentals in how the heart works from all possible aspects. This thesis aimed to profile the full landscape of A-to-I RNA editing in cardiomyocytes, from the point of view of differentiation as well as disease state–specifically IHD. The former was to see whether A-to-I RNA editing played a role in the formation of cardiomyocytes, whereas the latter was to see whether the mechanism played a role in the progression in the deadliest CVD. As the lack of cardiomyocyte regeneration proves to be an issue in CVDs, looking into how the mechanism affects cardiac differentiation might prove useful for future therapeutic attempts.

1.3. Hypothesis

The author hypothesized that there were going to be changes in RNA editing frequency as the cells differentiated across the timepoints, as well as difference in the editing site frequencies between control and IHD samples.