

Rheumatoid Arthritis (RA) is a chronic, inflammatory joint disease that is strongly associated with cardiovascular disease (CVD). CVD is the main cause of the excess morbidity and mortality risk in patients with RA. Patients diagnosed with RA may have cardiac problems within one year. Among people with RA, the risk of having a heart attack increases by 60 percent in one to four years after the RA diagnosis. The risk of other forms of coronary heart disease such as angina and coronary death increases by 50 percent in the same time frame. The most common heart disease risk factors in RA patients include high blood pressure, high cholesterol, high body mass index, and family history of heart disease. In addition, women with RA who go through menopause before age 45 have an increased risk of heart disease. Generally, the more severe the RA is, the more likely patients will develop cardiovascular problems, such as heart attack, stroke and heart failure.

Several factors may explain the increased CVD risk in RA, including systemic inflammation, accelerated atherosclerosis and administration of medications used to manage RA. However, assessing risk for heart disease in someone with RA can be challenging. For example, high inflammation sometimes causes cholesterol levels to drop, so a clinician may not think a person with RA is at risk for heart disease if the tests show low cholesterol. The same is true about weight - high inflammation is associated with weight loss, so again, a physician may think a lean person with RA has low cardiac risk.

In this project we wish to identify more specific mechanisms that might be associated with the development of heart disease in RA patients, such as damage to mitochondrial function and cellular metabolism. Mitochondria are the powerhouses of the cell, generating the energy needed for our cells to do their job. Studies have suggested that impaired mitochondrial functions and altered metabolic fingerprints may be useful in predicting the development of many human diseases, as well as in the evaluation of the treatment response. Therefore in this study we will examine the interplay between inflammation and mitochondrial metabolism in promoting cardiovascular complications in arthritis. Furthermore, we will test if currently available treatment strategies used in RA are protective or cytotoxic for cardiac cell functions. It will be investigated by using cardiac cells, joint cells and induced pluripotent stem cells (iPSC). iPSC are a type of stem cell that can be generated directly from adult cells. They have the same properties as embryonic stem cells, i.e. self-renewing and pluripotent differentiation giving rise to many other cell type, such as neurons, heart, pancreatic, and liver cells. The iPSC technology was pioneered by Shinya Yamanaka's lab in Kyoto, Japan, who was awarded the 2012 Nobel Prize. Nowadays, iPSC have become an important tool for modelling and investigating human diseases, for screening drugs and in the field of regenerative medicine.

Knowledge of the predictors of cardiovascular risk, the effects of inflammation-modulated mitochondrial functions and drug-specific effects will likely improve the recognition and management of cardiovascular risk in patients with RA. As CVD and RA share genetic and environmental risk factors, our goal is to describe whether "what is good for the heart is good for the joint and *vice versa*". Finally, the findings from our research may open a new avenue towards iPSC therapy trials for heart and joint diseases.