Cardiovascular Disease and Co-Morbidities

Cardiovascular diseases are complex beginning with some form of damage an artery that leads to inflammation and over time development of an atherosclerotic plaque. It is the rupture of these plaques that causes heart attacks and strokes. In today’s world, the risk of heart attacks and strokes is amplified by the increasing presence of other chronic diseases like kidney disease and diabetes. The Lab of Cooper Woods is interested in how this mechanistically happens, and what molecules could be used to clinically predict which patients are at greater risk for heart attacks and strokes and to prevent them. The lab uses both animal models to study the basic biology of CVD, as well as human samples from at-risk or post-stroke patients. This is fairly unique in this field, as most labs will focus on either the clinical side or animal modeling of the diabetes, but not both.

Basic Biology of CV Dysfunction in Diabetic Patients

Early in his career, Dr. Woods identified the aberrant expression of two miRNAs as a major cause of smooth muscle cell dysfunction in diabetic patients. These miRNAs were elevated in diabetic patients, causing the smooth muscle cells to proliferate and invade the artery. Additionally, they discovered that these dysfunctional smooth muscle cells can secrete exosomes, or small signaling particles derived from the cell filled with different proteins and RNAs. These exosomes are proinflammatory and can affect both the endothelial cells lining the artery as well as associated macrophages – exacerbating arterial thickening and increasing the risk of an eventual heart attack or stroke.

The Woods lab studies the basic biology and downstream targets of these miRNAs using an atypical mouse model created from a cross of a hyper-obese mouse with a pre-diabetic mouse. The resulting mice more closely mimic human patients as they display the appropriate expression levels of the miRNAs, where other diabetic mouse models are unable to recapitulate this miRNA expression. Thus, the lab is uniquely situated to study the cardiovascular complications of diabetes in a way that very closely mimics the molecular biology of the human disease.
Basic Biology of CV … (cont.)

Data from this mouse model is constantly compared to data from real human patients, ensuring that the two systems closely complement one another to accurately mimic human disease. Lastly, the lab is actively investigating the mechanics of wound healing in diabetic patients using a novel biomaterial derived from de-cellularized bladder tissue. Understanding these fundamental principles of cardiovascular dysfunction in diabetic patients will lead to better treatment options and the identification of better prognostic indicators.

Late-Stage Patients: Biomarkers & Predictive Models

While the two pivotal miRNAs in question are up-regulated during plaque buildup, they are sharply downregulated immediately prior to rupture and stroke. If this could be monitored (or controlled), we could more accurately predict what patients will actually have an event or even prevent an occurrence. To find appropriate biomarkers that will enable this, Dr. Woods works with a surgeon who obtains vascular tissue from patients both pre- and post-stroke. These samples are subjected to a variety of analyses, including second generation RNA sequencing to examine their transcriptomic profiles.

The lab believes there should be a subgroup in the pre-stroke population that more closely matches the post-stroke population than the other pre-stroke patients. Ideally, some of these genes could be used as testable biomarkers to predict which patients with arterial thickening are at risk of stroke and which are not. This is only possible due to the unique collaboration that lab has with a surgeon, allowing for unusual access to samples immediately post-stroke (~2 days) – as normally vascular surgery happens on the order of 2-3 weeks after the initial event.

In addition to transcriptomic profiling, serum is obtained from these patients in order to begin to identify biomarkers for stroke risk. One serum marker has already been potentially identified: a circular RNA that is responsible for downregulating the miRNAs so crucial for smooth muscle cell dysregulation in diabetes. This initial result neatly illustrates the overarching strength of this lab: an ability to link basic biology to a translational and clinically actionable outcome.

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