SÉMINAIRE DE L'AXE

Découverte et validation de cibles thérapeutiques

Cardiac Insulin Resistance in Heart Failure

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à l'invitation du professeur Rami Al Batran

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A burgeoning literature suggests a positive correlation between obesity (along with its associated insulin resistance) and heart failure development. However, recent studies have paradoxically suggested a better prognosis in overweight or mildly obese patients with pre-existing heart failure, known as the "obesity paradox". How obesity influences cardiac function, hypertrophy and energy metabolism in heart failure associated with obesity is not clear, and what effect weight loss has on these parameters is yet to be defined. Recent studies by our group showed that obesity causes an excessive reliance on fatty acid as a main source of energy in the failing heart and that obesity-induced high reliance on fatty acid oxidation exacerbates cardiac dysfunction and hypertrophy and does not improve cardiac ATP production. These studies also demonstrated that weight loss due to dietary intervention improves cardiac function, hypertrophy and energy metabolism in the obese failing heart. Weight loss-induced cardioprotection is mediated by enhancing cardiac insulin sensitivity signalling and insulin-stimulated glucose oxidation rates in the obese failing heart. Recognizing the role of cardiac insulin resistance in heart failure, we recently sought to characterize the cardiac insulin signalling pathway and how it influences cardiac glucose oxidation. We uncovered the molecular mechanism through which insulin directly stimulates mitochondrial glucose oxidation rates. These studies showed that insulin-stimulated mitochondrial Akt is a prerequisite in mediating the direct insulin stimulation of glucose oxidation in the heart, independent of enhancing glucose uptake and glycolysis. The study also unveiled a novel regulatory role for mitochondrial PKC-δ as a negative-feedback loop to inhibit insulin stimulation of glucose oxidation, and that inhibition of this loop mimics insulin stimulation of glucose oxidation. This exciting and uncharted area of investigation represents a potential therapeutic target to lessen the detrimental impact of cardiac insulin resistance in heart failure.