Abstract
Liver cancer is one of the most prevalent cancers worldwide and it is expected that the number of patients affected will rise in the future due to obesity and diabetes (1). Surgery involving resection of the affected liver is the cornerstone of treatment. One of the main problems in liver surgery however is the need to thoroughly control hemorrhage due to high liver blood supply provided by the portal vein and hepatic artery. Therefore, to be able to safely perform a resection, the surgeon needs to temporarily stop blood flow to the liver by clamping the portal vein and hepatic artery, a procedure called the Pringle maneuver. Its downside however is that it induces significant ischemia to the remnant liver. The real problem occurs when liver tissue that previously underwent ischemia is again perfused. During ischemia, mitochondria within liver cells become temporarily dysfunctional and unable to effectively cope with the burst of new oxygen delivered during reflow. Due to this dysfunction, a significant amount of reactive oxygen species is formed, inducing significant damage to all liver structures and exacerbating the damage already sustained during ischemia. This mechanism is called ischemia reperfusion injury (IRI) and is the main responsible for morbidity and mortality following liver surgery (2-6). Due to its clinical relevance, several preventive strategies have been explored but none has shown substantial benefits (7). The heart is one of the organs where IRI has been most studied. One of the strategies that renders the myocardium significantly more tolerant to IRI is previous exercise training (8-11). Several studies show that exercise preconditioning (the effect of exercise before IRI) stimulates the development of protective mechanisms that reduce myocardial damage and myocardial infarct area which has been suggested to result from favorable adaptations in the activity and expression of mitochondrial antioxidant enzymes (9). Since the mechanisms of IRI are, in essence, similar in different tissues, it could therefore be speculated that exercise pre-conditioning may also confer similar protective adaptations against liver IRI. Two recent studies using animal models have shown that, in rats with steatosis, previous exercise significantly reduces the extent of liver IRI (13,14). However, as exercise is known to reduce steatosis and this is a known risk factor for IRI it still remains undetermined if exercise effectively renders liver tissue more tolerant to ischemia and reperfusion or if the observed decrease in liver damage was due to a reduction in liver steatosis. More studies are therefore needed to determine if exercise is protective against liver IRI in situations without liver steatosis. The main aims of our proposal are therefore to determine if exercise reduces liver IRI and investigate the mechanisms potentially involved in these favorable adaptations. To accomplish this we will perform three experiments. In the first one, the aim is to determine if sedentary behavior prior to surgery increases the risk of liver IRI. We will compare liver damage in rats that were either sedentary or physically active before undergoing liver IRI. The main aim of our second experiment is to compare the degree of protection conferred by physical activity to ischemic pre-conditioning, which is one of the strategies to reduce liver IRI (12). The aim of our third experiment is to determine if high intensity exercise is more effective in reducing liver IRI compared to light intensity exercise or unrestricted physical activity. These experiments, will enable us to determine if, how and to what extent sedentary behavior, physical activity and exercise training of different intensities influences the degree of liver damage in IRI. Animals will undergo a period of 30 min of partial liver ischemia, in accordance with a previously established protocol (3) and 24h of reperfusion, during which blood samples will be collected to characterize liver damage. At sacrifice, the liver will be collected and thoroughly analyzed for determination of histological, ultrastructural and biochemical markers of damage, and assessment of mitochondrial function. In addition, we will investigate the mechanisms that could potentially explain the benefits of previous exercise on the reduction of liver IRI. To do so we will investigate the expression of potential candidates in key pathways of cellular metabolism, mitochondrial function and redox balance. We will also employ proteomics methods to perform an exploratory analysis of previously unrecognized pathways that might provide us more evidences regarding how sedentary behavior, physical activity and exercise might influence the extent of liver IRI. If our assumptions are correct, data resulting from this project can contribute substantially to reduce morbidity due to liver IRI and therefore greatly benefit patients undergoing liver resection surgery.