β, β-carotene 9',10'-oxygenase 2 in hepatic mitochondrial function and obesity

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The obesity epidemic is one of the most significant health challenges to the State of Oklahoma. In the rural areas of Oklahoma, lack of access to affordable fresh fruits and vegetables leads to an even higher level of obesity, compared to that in the urban areas. Fresh fruits and vegetables contain a variety of bioactive components, including but not limited to carotenoids that may have significant potentials to reduce the incidence of obesity. There are two carotenoid metabolic enzymes identified so far. β, β-carotene 9',10'-oxygenase 2 (BCO2) is a newly identified enzyme that catalyzes the asymmetric cleavage of carotenoids in mammals, whereas β, β-carotene 15,15'-monooxygenase 1 (BCMO1) symmetrically cleaves only pro-vitamin A carotenoids.

We recently generated a novel obesity model – the BCO2 knockout (KO) mouse. Under a regular growth condition, the KO mice are not obese when fed a standard chow (e.g., a low fat diet), though they consume more food than the wild type genetic background 129S6 (WT). However, they are more obese than WT when fed a high fat diet (45 % kCal from fat). Further, the process of obesity in KO mice could not be delayed by a high fat diet rich in carotenoids (e.g., a high fat diet with 5 % (w/w) spinach and/or wolfberry), indicating that BCO2 may be critical to obesity prevention (our unpublished data). Thus, the unique characters of this mouse model make it highly applicable to diet-induced obesity studies, in particular for those dietary studies on health consequences of a high fat diet with no or low greens as described above.

In this project, we speculate that BCO2 plays an essential role in maintaining the integrity of mitochondrial function in health and obesity, through targeting the electron transport chain. A decrease in BCO2 protein expression induced by a high fat diet will contribute to more severe proton leak, mitochondrial dysfunction, and cellular oxidative stress and inflammation, which eventually lead to obesity. Therefore, this project fits the priority areas of obesity prevention, rural community health challenge, food choices and disease prevention, and human nutrition and health disparities. It would potentially improve life of individuals in the rural areas of Oklahoma.

The ***long-term goal*** of the research project is to better understand how BCO2 regulated by carotenoid-enriched diets contributes to the integrity of mitochondrial function in the development of obesity, and to develop dietary interventions and treatment strategies against obesity. Because the liver is the center of nutrient metabolism, this seed grant will be focused on the fundamental function of BCO2 in the integrity of hepatic mitochondrial function in the liver of healthy and obese mice. Due to limited budget, no dietary fruits and/or vegetables will be tested at this point.

Our ***hypothesis*** for this seed grant is that a high fat diet-suppression of hepatic BCO2 protein expression causes disturbed integrity of mitochondrial function and subsequently triggers cellular oxidative stress and inflammation. Complete ablation of BCO2 causes those knockout mice to be more susceptible to a high fat diet-induced obesity due to more severe proton leak and subsequent damage to hepatic mitochondria. The following two specific objectives have been developed to test the hypothesis.

Objective 1: To determine how BCO2 controls the integrity of mitochondrial function (proton leak, ROS production, ETC complex activities, and ATP production) in WT and BCO2 KO mice fed a high fat diet

Objective 2: To characterize the role of BCO2 on global status of cellular oxidative stress and inflammation in a high fat diet-induced obese mice (WT vs KO) via a metabolomic approach.