

Cardiovascular disease (CVD) and Alzheimer's disease (AD) are the major public health issues in industrialized societies. Because known risk factors do not accurately predict CVD or AD, identification of novel risk factors and their mechanisms of action have important public health implications. Elevated level of homocysteine (Hcy) is an emerging risk factor for CVD and AD. However, mechanisms underlying the involvement of elevated Hcy in these diseases are not fully understood. In our previous studies we found that a chemically reactive and toxic Hcy metabolite, Hcy-thiolactone, damages proteins in the human body by generating a KHcy modification at proteins' lysine residues. The KHcy protein modification has been linked to inflammation, thrombosis, stroke, CVD, and AD. Our present study examines the KHcy modification in histone proteins, important for proper gene expression, in the heart and brain using mouse models with elevated Hcy.

Our hypothesis is that histone KHcy modification is induced by elevated Hcy, a clinical feature associated with heart and brain diseases; this alters normal histone function and leads to disease. We will elucidate patterns of histone KHcy modifications and how they impair normal histone modifications (acetylation/methylation) in the heart and brain. We will examine these modifications in histones bound at regulatory regions of mouse brain genes whose impairment has been linked to several neurological diseases in humans, including AD. We will also study a role of a neuroprotective enzyme, Blmh, in histone modifications and gene expression in the mouse brain.

Mapping histone KHcy sites in the heart and brain and elucidating how they affect homeostasis of histone acetylation/methylation is an important prerequisite for understanding their role in heart and brain diseases. Because histone modifications are conserved between mice and humans, our findings will be applicable to humans. Our proposed novel applications of the mass spectrometry technology to quantify the KHcy modification at all lysine sites across each histone *in vivo* will provide important insights into their role in health and disease with implications for treatment and prevention.