



**Shriners Hospitals** for Children®  
Boston, Massachusetts

## **BURN-INDUCED METABOLIC DYSFUNCTION AND INFLAMMATORY RESPONSE**

Burn-induced severe metabolic derangements (called burn cachexia) increase the morbidity and mortality and interfere with the recovery and wound healing in patients who have been burned. Burn cachexia can cause cardiovascular dysfunction and impair immune function, rendering patients susceptible to infection and sepsis (severe infection and the major cause of mortality of burn patients). Like cancer cachexia, in some cases of burn cachexia can cause multiple organ dysfunction and can lead to death. Therefore, the clinical priority of finding a way to reverse these burn-induced metabolic derangements is high. Despite decades of research, new treatments that target stress-induced insulin resistance (a denominator of burn-induced metabolic aberration) or metabolic dysfunction have not been developed for critical illness (e.g., burn injury).

The research team at Shriners Hospitals for Children — Boston has previously shown that control of inflammatory response by inhibition of inducible nitric oxide synthase and protein farnesylation prevents the development of metabolic dysfunction and insulin resistance in a mouse model of burn injury (Figure 1) (References 1, 3, 4). These studies are designed to pave the road to develop clinical trials of these inhibitors for the evaluation of the safety and efficacy to improve the clinical outcome of burn patients. Moreover, our research indicates that protein S-nitrosylation (the covalent attachment of nitric oxide to cysteine thiols) plays an important role in the inflammation-mediated pathogenesis of many human diseases (Figure 2) (Reference 2), which include burn injury and sepsis. These studies enhance our understanding of how and when inflammation becomes pathogenic contributing to the development of human diseases, whereas inflammatory response itself is adaptive in nature, and thereby help identify molecular targets to properly control inflammatory response.

### **Recent Publications**

1. Nakazawa H, Yamada M, Yu Y-M, Fischman AJ, Martyn JAJ, Ronald. G. Tompkins RG, Kaneki M. Role of protein farnesylation in burn-induced metabolic derangements and insulin resistance in mouse skeletal muscle, PLOS ONE, 2015 Jan 16;10(1):e0116633. PMID: 25594415
2. Shinozaki S, Chang K, Sakai M, Shimizu N, Yamada M, Tanaka T, Nakazawa H, Ichinose F, Yamada Y, Ishigami A, Ito H, Ouchi Y, Starr ME, Saito H, Shimokado K, Stamler JS, Kaneki M. Inflammatory stimuli induce inhibitory S-nitrosylation of the deacetylase SIRT1 to increase acetylation and activation of p53 and p65. Sci Signal. 2014 Nov 11;7(351):ra106. PMID: 25389371
3. Kaneki M, Fukushima Y, Shinozaki S, Fukaya M, Habiro M, Shimizu N, Chang K, Yasuhara S, Martyn JAJ. iNOS inhibitor, L-NIL, reverses burn-induced glycogen synthase kinase-3 $\beta$  activation in skeletal muscle of rats. Metabolism. 2013 Mar;62(3):341-6. PMID: 22995863; PMCID: PMC4090935
4. Sugita M, Sugita H, Kim M, Mao J, Yasuda Y, Habiro M, Shinozaki S, Yasuhara S, Shimizu N, Martyn JAJ, Kaneki M. Inducible nitric oxide synthase deficiency ameliorates skeletal muscle insulin resistance but does not alter unexpected lower blood glucose levels after burn injury in C57BL/6 mice. Metabolism. 2012 Jan;61(1):127-36. PMID: 21816442; PMCID: PMC3304504
5. Yang W, Yamada M, Tamura Y, Chang K, Mao J, Zou L, Feng Y, Kida K, Scherrer-Crosbie M, Chao W, Ichinose F, Yu YM, Fischman AJ, Tompkins RG, Yao S, Kaneki M. Farnesyltransferase inhibitor FTI-277 reduces mortality of septic mice along with improved bacterial clearance. J Pharmacol Exp Ther. 2011 Dec;339(3):832-41. PMID: 21873557; PMCID: PMC3226365

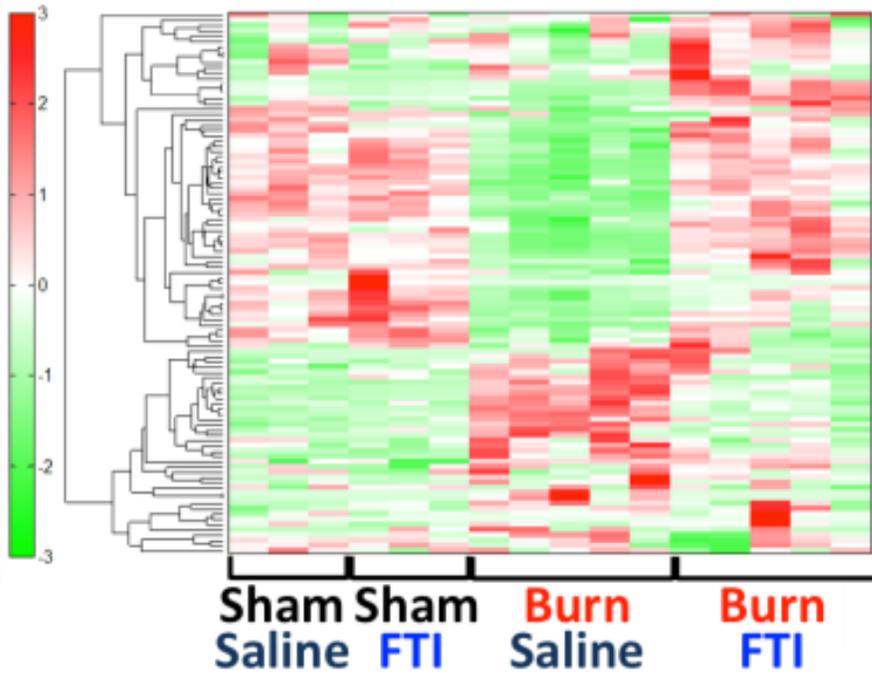


Figure 1. Metabolome analysis of skeletal muscle in burned and sham-burned mice treated with and without farnesyltransferase inhibitor (FTI).

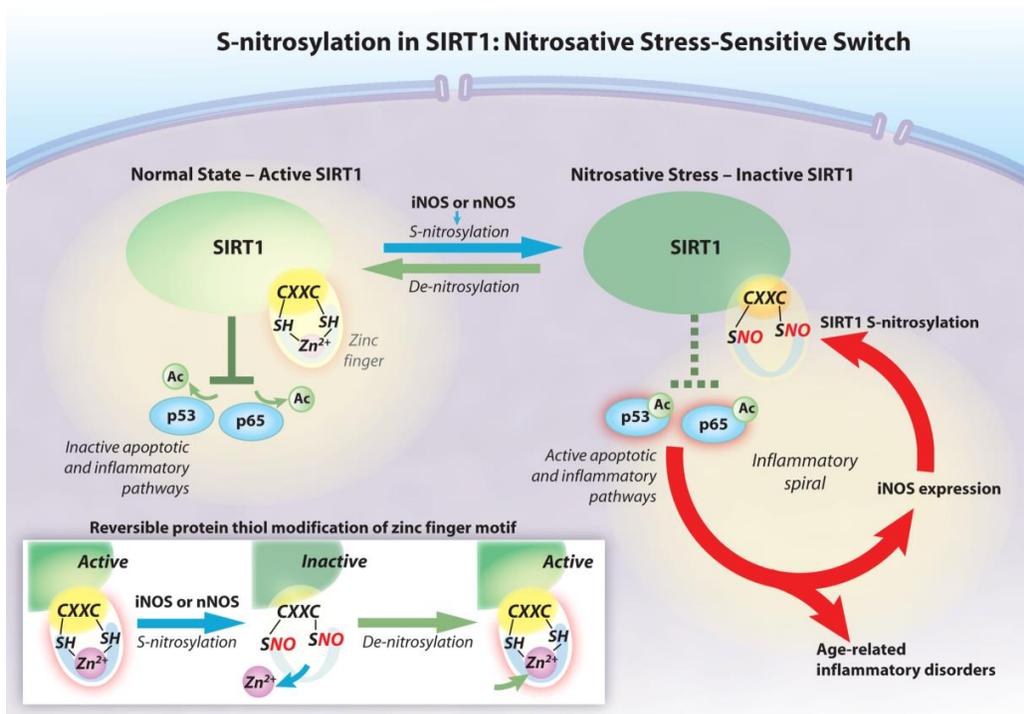


Figure 2. The proposed SIRT1 nitrosative stress-sensitive switch. (Sci. Signal. 2014; 7(351): ra106) Images provided by Masao Kaneki, M.D., Ph.D.