

様式 2

論 文 要 旨

論 文 題 目

**Nmnat3 gain-of-function protects against diet- and aging-associated insulin resistance in mice.****First department of Internal Medicine****Graduate School of Medicine and Pharmaceutical Sciences****University of Toyama**氏名 Maryam Gulshan

**Introduction:** Nicotinamide adenine dinucleotide (NAD) is an essential co-factor involved in numbers of metabolic enzymatic reactions. NAD also serves as a substrate for poly (ADP-Ribose) polymerases (PARPs) and NAD-dependent deacetylases (Sirtuins), and plays key roles in many cellular processes. Therefore, it is considered that intracellular NAD level critically regulates wide range of cellular functions in response to nutrient conditions. In organisms, NAD can be synthesized by de novo and salvage pathways. In salvage pathway, nicotinamide (NAM) is converted to nicotinamide mononucleotide (NMN) by Nampt (Nicotinamide phosphoribosyltransferase), and then nicotinamide mononucleotide adenylyltransferase (Nmnat) generates NAD from NMN. The aim of this study is to investigate the effect of over expression of Nicotinamide Mononucleotide Adenylyltransferase (Nmnat3) gene in diet induced obesity as well as in age induced obesity and glucose intolerance using mice model. **Methods:** Nmnat3 over expressed mice (Nmnat3 Tg mice) were employed and fed high fat diet (HFD) and normal chow diet for 18 weeks and 24 months respectively. Body weight of mice was also measured during this period of age. For assessing the metabolic status, intraperitoneal insulin tolerance test (IP-ITT) and intraperitoneal glucose tolerance test (IP-GTT) along with serum insulin level by Elisa, were performed after high fat diet- and age-induced obesity. Various tissues were harvested from 18 weeks HFD fed mice as well as from 4 , 18 and 24 months normal chow fed mice for LC-MS/MS metabolomics analysis. **Results:** Interestingly, overexpression of Nmnat3 was associated with increased intracellular NAD level in various tissues even after high fat diet- and age- induced obesity conditions. In addition to this enhancement of NAD

in Nmnat3 TG mice protected against insulin resistance, thus presenting a better metabolic outcome.

**Conclusion:** Our study suggest that Nmnat3 has a beneficial role against Diet-induced and age-induced obesity thus contributing to the improvement of the insulin resistance.