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## Dual targeting of Nur77 and AMPK $\alpha$ by isoalantolactone inhibits adipogenesis

Syng Ook Lee, Yeon Seop Jung and Hyo Seon Lee  
Keimyung University, Republic of South Korea

Suppression of adipogenesis has been considered as a potential target for the prevention and treatment of obesity and associated metabolic disorders, and the nuclear receptor 4A1 (NR4A1/Nur77) and AMPK $\alpha$  are known to play important roles during early and intermediate stages of adipogenesis. Therefore, we hypothesized that dual targeting Nur77 and AMPK $\alpha$  would show strong inhibitory effect on adipogenesis. We screened a herbal medicine-based small molecule library to identify novel natural compounds dual targeting Nur77 and AMPK $\alpha$ , and the antiadipogenic effects and mechanisms of action of a “hit” compound were studied in 3T3-L1 cells. We identified isoalantolactone (ISO) as a new NR4A1 inactivator that also activates AMPK $\alpha$  in 3T3-L1 cells. ISO, as expected, inhibited adipogenic differentiation of 3T3-L1 preadipocytes, accompanied by reduced mitotic clonal expansion (MCE) which occurs in the early stage of adipogenesis and decreased expression of genes required for MCE and cell cycle markers including cyclin A, cyclin D1. These results suggest that ISO dual targeting Nur77 and AMPK $\alpha$  during adipogenesis represents a novel class of mechanism-based antiadipogenic agents for treatment of obesity and associated metabolic disorders, including hyperlipidemia and fatty liver.

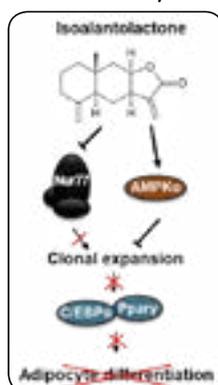


Figure 1. Schematic diagram illustrating inhibition of adipogenesis via dual targeting of Nur77 and AMPK $\alpha$  by ISO.

### Recent Publications:

1. Lee S O et al. (2010) Inactivation of the orphan nuclear receptor TR3/Nur77 inhibits pancreatic cancer cell and tumor growth. *Cancer Res.* 70 (17):6824-6836.
2. Lee S O (2012) The nuclear receptor TR3 regulates mTORC1 signaling in lung cancer cells expressing wild-type p53. *Oncogene.* 31(27):3265-3276.
3. Lee S O (2014) The orphan nuclear receptor NR4A1 (Nur77) regulates oxidative and endoplasmic reticulum stress in pancreatic cancer cells. *Mol. Cancer Res.* 12(4):527-538.
4. Hwang E Y et al. (2016) Defatted safflower seed extract inhibits adipogenesis in 3T3-L1 preadipocytes and improves lipid profiles in C57BL/6J ob/ob mice fed a high-fat diet. *Nutr. Res.* 36(9):995-1003.
5. Lee H S, Safe S and Lee SO (2017) Inactivation of the orphan nuclear receptor NR4A1 contributes to apoptosis induction by fangchinoline in pancreatic cancer cells. *Toxicol. Appl. Pharmacol.* 332:32-39.

### Biography

Syng Ook Lee focuses his research on the molecular biology of NR4A orphan nuclear receptors and the development of new mechanism-based drugs targeting NR4As for treatment of cancers and metabolic diseases. His research interest: targeting nuclear receptors for treating cancer and metabolic diseases.

synglee@kmu.ac.kr