PO-13

doi: 10.14232/tnpr.2019.po13

A novel pyruvate dehydrogenase kinase inhibitor hemistepsin A increases mitochondria-dependent apoptosis of colorectal cancer

Ling Jin[1,2], Eun-Yeong Kim[1,2], Tae-Wook Chung[2], Jung-Hee Lee[2], So Young Park[3], Jung Ho Han[2], Jong Rok Lee[4], Young Woo Kim[5], Se Bok Jang[3], Kibong Kim[5] and Ki-Tae Ha[1,2]*

[1] Department of Korean Medical Science, School of Korean Medicine, Graduate Training Program of Korean Medicine for Healthy-aging, and [2]Healthy Aging Korean Medical Research Center, Pusan National University, Yangsan, Gyeongsangnam-do 50612, Republic of Korea
[3] Department of Molecular Biology, College of Natural Sciences, Pusan National University, Geumjeong-gu, Busan 46241, Republic of Korea
[4] Department of Pharmaceutical Engineering and [5]College of Korean Medicine, Daegu Haany University, Gyeongsan, Gyeongsangbuk-do 38610, Republic of Korea
[5] 2nd Division of Clinical Medicine, School of Korean Medicine, Pusan National University and Pediatric, Korean Medicine Hospital, Pusan National University Hospital, Yangsan 626-870, Republic of Korea
E-mail: jinling0122@icloud.com

Most cancer cells primarily produce their energy through a high rate of glycolysis followed by lactic acid fermentation even in the presence of abundant oxygen. This phenomenon is called Warburg effect, also known as aerobic glycolysis, was firstly reproted by Warburg in 1920s. Pyruvate dehydrogenase kinase (PDK) 1, a kinase which inactivates the enzyme pyruvate dehydrogenase (PDH), is commonly overexpressed in tumors and recognized as a novel therapeutic target in colon cancer. Suppression of PDH by PDK1 prevents the conversion of cytoplasmic pyruvate into acetyl-CoA and then cytoplasmic pyruvate is converted into lactate even in the presence of oxygen presenting an advatage for cancer growth. Here, we report hemistepsin A, as a novel PDK kinase inhibitor, decreases PDK activity by binding to the lipoamide-binding domain of PDK1 without affecting its expression. Hemistepsin A is a sesquiterpene lactone isolated from *Hemistepta lyrata* Bunge (Compositae). *H. lyrata* has been used for the treatment of colon disease, such as diarrhea, hemafecia, and anal fistula, in traditional medicine of Eastern Asia. We demonstrate that hemistepsin A has anti-cancer effect on several colorectal cancer cells. After treatment with hemistepsin A, lactate production was markedly decreased. In the meantime, intracellular reactive oxygen species (ROS) levels and mitochondrial damages were increased. In addition, apoptosis was promoted with enhanced activation of caspase-3 and -9, improved cleaved PARP, enhanced level of Bax expression, decreased Bcl-2 expression. In *in vivo* mice models inoculated with CT26 colon carcinoma, hemistepsin A effectively suppressed tumor growth as determined by the reduction of tumor volume and weight, inducing by inhibiting the PDK1 activity but not by its expression. Taken together, we suggest that hemistepsin A suppresses growth of colorectal cancer through inhibiting activity of PDK1.

Acknowledgements
This work was supported by a grant from the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT & Future Planning (MISP), of the Korean Government (Grant no. 2014R1A5A20009936).