2009년도 춘계 학술발표회 논문집
대한방사선방어학회

Fenofibrate is radioprotective via SOD induction in HeLa cells

Xianguang Liu[1], Zhengzhe An[1], Won Dong Kim[1], Jae-Ran Yu[2] and Woo-Yoon Park[1]
[1] Department of Radiation Oncology, Chungbuk National University College of Medicine
[2]Department of Environmental and Tropical Medicine, Konkuk University College of Medicine
E-mail: wynpark@chungbuk.ac.kr

Key words : Ionizing radiation, Fenofibrate, Superoxide dismutase

Introduction

The fibrates are ligands for peroxisome proliferator-activated receptor (PPAR) α and used clinically as hypolipidemic drugs [1]. The fibrates are known to cause peroxisome proliferation, enhance superoxide dismutase (SOD) expression and catalase activity [2]. The antioxidant actions of the fibrates may be radioprotective. However, there is no report about it. Here, we investigated the change of the radiation sensitivity in cervix cancer cells combined with fenofibrate (FF).

Materials and Methods

The HeLa cells were incubated with various concentration of FF for 48 h. Superoxide dismutase activity was assayed using an assay kit (Dojindo, Gaithersburg, MD, USA). Protein expression was measured with Western blot. mRNA expression was measured with realtime PCR. Intracellular production of ROS was measured using the fluorescent dye, 2',7'-dichlorodihydrofluorescein-diacetate (H_2DCFDA). Combined cytotoxic effect of FF and radiation was measured using clonogenic assay.

Results and Discussion

Effect of FF on total SOD and catalase activity. Total SOD and catalase activity was measured in HeLa treated with various doses of FF for 48 h. Total SOD activity was increased with increasing FF doses and it was maximal at 30 μM of FF: about two times higher than control. The catalase activity was a little bit increased up to 10 uM. However, it was declined with higher FF doses.

Effect of FF on SODs and catalase protein induction. To investigate whether the SOD and catalase activity is related with their protein expression, Western blot was done for SOD1, SOD2 and catalase in HeLa cells treated with various doses of FF for 48 h. As with the activity the protein expression of SOD1 and SOD2 were increased with increasing doses of FF (up to 60 μM) and that of catalase was decreased with increasing doses (30 and 60 μM) of FF.

Effect of FF on SODs mRNA induction. To investigate whether protein expression of SOD1 and SOD2 is related with their mRNA induction, HeLa cells were treated with FF and real time RT-PCR was done. Both mRNA of SOD1 and SOD2 were increased with increasing doses of FF. This suggests increased protein expression of SOD1 and SOD2 by FF are caused from their mRNA induction.

Effect of FF on PPARα mRNA induction. To investigate whether protein expression of SOD1 and SOD2 is related with PPARα mRNA induction, HeLa cells were treated with FF and real time RT-PCR was done. PPARα mRNA was increased with increasing doses of FF. This suggests increased protein expression of SOD1 and SOD2 by FF are related with PPARα mRNA induction.

Intrinsic ROS and ROS produced by irradiation are effectively scavenged in the FF-pretreated HeLa cells. To investigate whether SOD induced by FF contributes to scavenge ROS, HeLa cells were treated with 10 μM of FF for 48 hrs and irradiated with 4 Gy. ROS produced by 4 Gy was decreased in the cells treated with FF.

FF decreases radiation-induced cell death of HeLa cells. Finally, we were interested in whether FF modifies radiation sensitivity by scavenging ROS. HeLa cells were treated with 10 μM of FF for 48 h and irradiated. The survival fraction (SF) by 4 Gy and FF alone were 0.062 and 0.80, respectively. The SF by combining FF and 4 Gy was 0.16, which is 3.2 times higher than expected value (0.050) on the assumption of simple each additive effect on SF. The radioprotective effect was observed in other doses (2, 8 Gy).

Conclusion

FF can reduce radiation sensitivity by ROS scavenging via SOD induction.

References

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