Thioredoxin/TRX-Dependent Redox Regulation of Inflamamatory Process

Junji Yodoi[1,2] Norihiko Kondo[1], Hiroshi Masutani[1], and Hajime Nakamura[2]

[1]Department of Biological Responses, Institute for Virus Research, Kyoto University, Kyoto University, 53 Shogoin, Kawahara-cho, Sakyo, Kyoto 606-8507,Japan
[2]Thioredoxin Project, Translational Research Center Kyoto University Hospital, 54 Shogoin, Kawahara-cho, Sakyo, Kyoto 606-8507, Japan

Thioredoxin (TRX) is a small thiol-mediated protein with a redox active disulfide/dithiol group within the conserved active site sequence Cys-Gly-Pro-Cys. TRX was originally cloned as an adult T-cell leukemia (ATL)-derived factor (ADF) has cytokine-like activity from human T-cell leukemia virus-I (HTLV-I) transformed T-cells. The expression of TRX is induced by a variety of oxidative stress including virus infection, and has been shown to play crucial roles in the regulation of cellular responses such as gene expression, cellular proliferation and apoptosis[1)]. Moreover, TRX in extracellular also regulates cellular responses induced many stimulations[2,3)]. Especially, we recentry start the TRC Translational Research Project in Kyoto Univ Hospital TRC/Translational Research Center, aiming for the clinical application of administration of TRX for acute lung disorders and redox regulating drug discovery.

As the mechanisms of TRX-dependent regulation of cellular responses are still unclear, we generated TRX-C35S, which is displaced in redox-active site to clarify the TRX membrane traffic mechanism. Unexpectedly, TRX-C35S entered rapidly into HTLV-I-transformed T Cells via the Lipid Raft System, which is composed of caveolae containing caveolin-1 protein as well as the activated T cells expressing CD25/IL-2R-alpha. Lipid rafts fraction of Jurkat T cells activated by PMA/Ionomycin or anti-CD3 antibody was increased to internalize this molecule than resting Jurkat cells. These results suggest that extracellular TRX can enter intracellular compartment via unique Lipid Rafts pathway regulating cellular redox status.

We identified thioredoxin-binding protein-2/vitamin D3 up-regulated protein 1 (TBP-2/VDUP1) as a negative regulator of TRX. Expression of TBP-2 was completely abolished in HTLV-I-positive IL-2-independent cells, whereas that of TRX was markedly enhanced. TBP-2 stably interacted with TRX *in vivo* and *in vitro* and has an inhibitory effect on TRX dependent reducing activity. Further, ectopic overexpression of TBP-2 in HTLV-I-positive T cells resulted in growth suppression in association with a G1 cell cycle arrest, an increase of p16, and reduction ob RB phosphorylation[4)]. These results suggest that TBP-2 plays a crucial role in the growth regulation of

T-cells through the interaction with its target molecules including TRX

Refferences

1) Annu. Rev. Immunol. 15, 351-369, 1997

2) Proc. Natl. Acad. Sci. USA 96, 4131-4136, 1999

3) Proc. Natl. Acad. Sci. USA 98, 15143-15148, 2001

4) Cancer Res. 64, 1287-1292, 2004