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Peroxiredoxins in inflammatory liver diseases and ischemic/reperfusion injury in liver transplantation

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ABSTRACT

Peroxiredoxins (Prxs) belong to the superfamily of thiol-dependent peroxidases, and remove reactive oxygen species (ROS) and other oxidative stress products. The expression and activity of Prxs can be substantially affected by stimuli from the microenvironment, and in turn regulate cytokine secretion in the context of inflammation in both peroxidase-dependent and -independent pathways. Prxs translocate to mitochondria and are hyperoxidized during acute liver damage, and attenuate intracellular ROS accumulation through their peroxidase activity. In particularly, Prx1 modulates the microenvironment in liver injuries by reducing adhesion molecule expression in vascular endothelial cells and inhibiting the inflammatory response and adhesion of macrophages. Prxs have potent prosurvival effects against ROS in ischemic/reperfusion (I/R) injury, but Prxs released from necrotic cells increase secretion of inflammatory cytokines by macrophages through TLR2 and 4 activation, which promotes cell death. Prxs can be used as biomarkers to evaluate I/R injury and predict graft survival in liver transplantation. Prxs are modulated in various types of chronic hepatitis and hepatosteatosis, and mediate disease progression. Alcohol administration increases oxidization and inactivation of Prxs in mice because of oxidative stress. In conclusion, Prxs are essential mediators and biomarkers in inflammatory liver diseases and I/R injury.

1. Introduction

Metabolism produces a large amount of reactive oxygen species (ROS), including H_2O_2, hydroxyl radicals, and superoxide anion, which might subsequently elicit changes in the structure/function of biological macromolecules, such as lipid peroxidation, protein and nucleic acid oxidation, and DNA rupture. Overwhelming ROS accumulation promotes cell apoptosis and tissue necrosis (Wang et al., 2011; Xu et al., 2012). To survive in the hazardous environment created by these ROS-like substances, organisms have developed various types of antioxidant systems, such as catalase, superoxide dismutase, glutathione peroxidase, and thioredoxin (Trx) oxidase (peroxiredoxin; Prx) during evolution. Prxs, which belong to the superfamily of thiol-dependent peroxidases, were first characterized in the yeast *Saccharomyces cerevisiae* about 30 years ago (Kim et al., 1989). Unlike other antioxidant enzymes, Prxs do not contain a reducing co-factor, such as Fe^{2+} or ferrihemoglobin. Instead, Trx acts as an intermediate H^+ donor to neutralize peroxides (Chae et al., 1994). Prxs exist in almost all organisms, particularly in the cytoplasm (Poynton and Hampton, 2014), accounting for 1% of soluble proteins (Wood et al., 2003). As endogenous biomarkers of oxidative stress, Prxs participate in cellular signaling pathways and play essential roles in numerous cellular functions including apoptosis and proliferation.

Six types of Prxs (Prx1–6) have been identified in mammals (Nelson et al., 2011). They can be further categorized into two subtypes based on the number of conservative cysteine residues. Prx1–5 have two conservative cysteine residues to catalyze H_2O_2 and are therefore called 2-Cys Prxs. Prx6 (also called 1-Cys Prx) has only one conservative cysteine residue. Prx1, 2, and 6 are mainly localized in the cytoplasm. Prx3 is dominantly found in mitochondria, while Prx5 is widely spread

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Abbreviations

ROS	reactive oxygen species
DNA	deoxyribonucleic acid
Prx	Peroxiredoxin
NK	nature killer
IFN-γ	Interferon-γ
LPS	Lipopolysaccharide
TRIF	Toll/IL-1R domain-containing adapter-inducing IFN-β
MyD88	myeloid differentiation primary response gene (88)
TNF	tumor necrosis factor
PLA2	Phospholipase A2
NOX2	NADPH oxidase 2
Ncf1	Neutrophil cytosolic factor 1
TLR-4	Toll like receptor 4
JAK2	Janus Activating Kinase 2
I/R	Ischemic/Reperfusion
Trx	thioredoxin
NKEF	NK cell enhancement factor
CYP2E1	Cytochrome P450 2E1
NAFLD	non-alcoholic fatty liver diseases

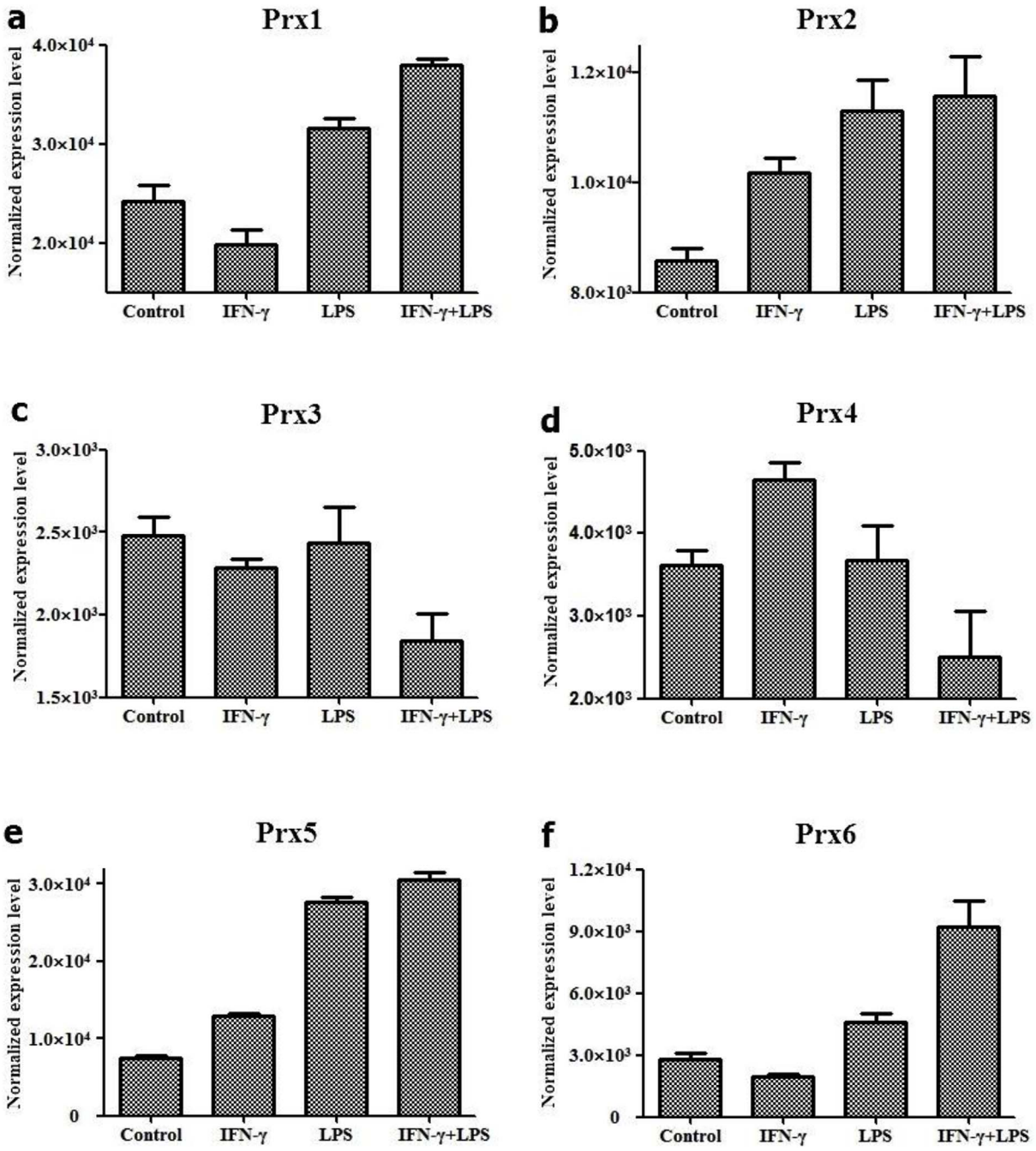

Fig. 1. Changes of Prx expression (normalized expression level, mean ± SEM) in bone marrow-derived macrophages after stimulation with LPS and/or IFN-γ (GDS5196, n = 16).