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Thiol redox barrier; local and systemic surveillance against stress and inflammatory diseases

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ABSTRACT

A 12-kDa protein with redox-active dithiol in the active site -Cys-Gly-Pro-Cys-, human thioredoxin 1 (TRX) has demonstrated an excellent anti-inflammatory effect in various animal models. TRX is induced by various oxidative stress factors, including ultraviolet rays, radiation, oxidation, viral infections, ischemia reperfusion and anticancer agents, and are involved in the pathogenesis and progression of various diseases. We have demonstrated that systemic administration and transgenic overexpression of TRX is effective in a wide variety of in vivo inflammatory disease models, such as viral pneumonia, acute lung injury, chronic obstructive pulmonary disease, indomethacin-induced gastric injury, and dermatitis. Our recent studies indicate that topically applied TRX prevents skin inflammation via the inhibition of local formation of inflammatory cytokines and chemokines. These indicate that the activation of inflammasome in skin and mucosa may be regulated by TRX. These suggest that application of TRX may be useful for the treatment of various skin and mucosal inflammatory disorders. Based on these results, we are conducting clinical studies to develop human recombinant thioredoxin 1 (rhTRX) pharmaceuticals. We have also developed substances that increase the expression of TRX in the body (TRX-inducing substances) in vegetables and other plant ingredients, and we are also developing skin-care products and functional foods that take advantage of the anti-inflammation and anti-allergic action of TRX.

1. Introduction

1.1. What is thioredoxin?

During our long years of work on human viral disease Adult T Cell Leukemia (ATL), which we initially described in Kyoto in the early 1970's along with Dr. Kiyoshi Takatsuki and our work on allergies to modulate IgE responses with Drs. Kimishige and Teruko Ishizaka, who had opened the Institute for Immunology at Kyoto University, we discovered the redox regulating protein human thioredoxin 1 (TRX) as a soluble regulator ATL-Derived Factor (ADF) at the end of the 1980s [1] (Fig. 1). ADF is human TRX, which has more than 30 family members with the dithiol consensus sequence of C-X-Y-C with oxide-reductase activity. Several active research groups, including Drs. Hiro Wakasugi and Thomas Tursz in Paris, independently confirmed the existence of TRX and the related redox regulatory molecules.

1.2. The influence of Dr. Helmut Sies on our studies

Our redox biomedical research was based on our studies of Thiol TRX molecules, together with the work conducted by Dr. Arne Holmgren in Karolinska and others who were recognized by Oxygen and Free Radical Research, which was led by Dr. Helmut Sies and Dr. Lester Packer, who opened the field of redox biology in health and medical science at the end of the 1990s (Fig. 2). The expression of TRX is induced by a variety of natural substances and plant products such as GGA/Geranyl–geranyl, sulphoraphane, and estrogen. While Syngenta once pushed the world-distribution of "Golden rice" designed to raise the production of beta carotene, they were more interested in producing rice than producing recombinant TRX.

These fields are closely related to the areas studied by Helmut Sies and other OCC members.

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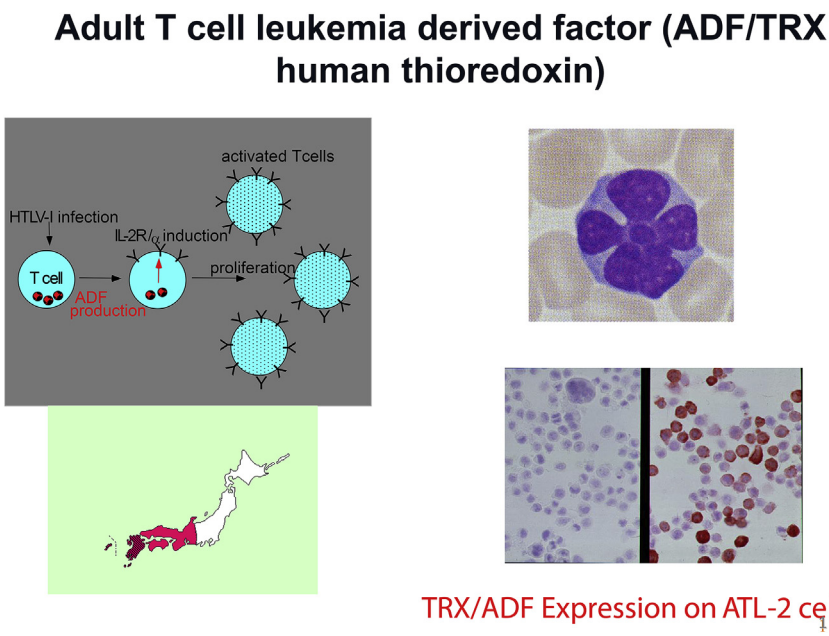

Fig. 1. Human TRX was cloned as adult T-cell leukemia–derived factor produced by human lymphotropic virus type I–transformed T cells.

Fig. 2. Dr. Helmut Sies visited our lab in Kyoto University, where we had a good discussion on anti-oxidants and redox signaling.

1.3. Dr. Helmut Sies contributed greatly to the research fields of redox, oxygen and free radials

The Journal *Anti-Oxidants and Redox Signaling (ARS)* was one of the earliest Redox Biomedical Journals connecting the Redox Signal Area and Anti-Oxidant Research. Today, there are many redox-related journals, including *Redox Biology*, which is based on FRBM, that have contributed to our knowledge of the pertinent fundamental relationships in the fields of redox, oxygen and free radicals (Fig. 3).

We consulted with Dr. Helmut Sies in many meetings held by the Oxygen Club of California (OCC), which was initiated by Lester Packer, Helmut Sies and Enrique Cadenas. Studies in the redox biomedical and health science fields were accelerated by the International Redox Network (IRN) (Fig. 4). This vital international network was initiated in 2004 in Stockholm after several important international redox meetings were held from 1996, with participation by Luc Montagnier, Lester Packer and essentially all the leading figures in the redox biomedical fields (Fig. 5).

1.4. Our research on TRX family proteins

Today it is widely accepted that Thioredoxin family proteins play key roles in redox regulation in both cells and tissue. While many investigators have basically been concerned with the intracellular roles of redox regulation, we have clearly focused on the roles of TRX in the extracellular environment, as a type of intercellular regulator molecule. Indeed, human TRX was discovered as a ADF/ATL-derived factor released from human cells [1]. This serendipity-like accidental finding was shared by several other research groups, including that of Thoma Tursz and Hiro Wakasugi in Paris. We have demonstrated that exogenous TRX is effective in a wide variety of in vivo inflammatory disease models, such as viral pneumonia, acute lung injury, gastric injury, and dermatitis (Fig. 6). In the following section, we will describe some of the findings related to the protective effects of applied exogenous TRX in some inflammatory disease models.

2. Respiratory disease

In a previous study, we showed that the intraperitoneal administration of recombinant human thioredoxin (rhTRX) alleviates interstitial pneumonia caused by the anticancer agent bleomycin, as well as some acute pulmonary disorders accompanying cytokinemia [2]. Furthermore, we demonstrated that the intravenous administration of rhTRX inhibited the extravascular transudation of leukocytes to inflammation sites and also that it inhibited ischemic reperfusion disorders of the lungs [3]. In addition, we demonstrated that the intra-peritoneal administration of rhTRX suppressed chronic obstructive pulmonary disorders induced by cigarette smoke, as well as influenza A virus (H1N1)-induced acute lung injury in mice [4,5].

3. Gastric injury

We developed yeast-derived TRX and used it in the treatment of gastric injury produced by the intraperitoneal administration of indomethacin, which is one kind of nonsteroidal anti-inflammatory drug, in mice. Prior to the administration of indomethacin, the mice