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Multiple targets of carbon monoxide gas in the intestinal inflammation

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ABSTRACT

Inflammatory bowel diseases (IBDs) such as ulcerative colitis and Crohn's disease are chronic relapsing and remitting inflammatory disorders of the intestinal tract. It is important to investigate the precise pathogenesis of IBD, to evaluate new anti-inflammatory agents, and to develop novel drugs. Carbon monoxide (CO) has emerged as an important regulator of acute and chronic inflammation of the gastrointestinal tract. The mechanism underlying its anti-inflammatory effects is only partially understood. Recent reports have demonstrated that CO could play a role in the functional modulation of epithelial and immunological cells in the intestine. In this short review, we have highlighted the recent findings that CO stimulates the epithelial cell restitution and FGF production from myofibroblasts. CO was also shown to regulate T cell activation and differentiation, and to activate macrophages. Finally, we have discussed the direction of translational research with respect to launching a novel agent for releasing CO in the intestine.

1. Introduction

In 1988, the fourth biennial meeting of SFRR International was held at Kyoto in Japan (President: Osamu Hayaishi, Chairman: Etsuo Niki, Secretary-General: Toshikazu Yoshikawa) with the idea of enrolling more Asian and Japan members. Holding this Kyoto meeting developed the study of this field drastically in Japan. Prof. Helmut Sies was supporting our committee members efficiently in many ways, not only during the meeting, but also the preparation period (Fig. 1). We would like to emphasis our deep appreciation on his effort. At the occasion of 10th and 17th biennial Meeting of SFFRI in Kyoto in 2000 and 2014, his participation and presentation contributed great benefit continuously to the progress of this field in Japan. In addition, he delivered an invited lecture entitled “High selenium intake and increased diabetes risk: experimental evidence for interplay between selenium and carbohydrate metabolism” at the International Symposium on Free Radical Research: contribution to Medicine in Celebration of Prof. Toshikazu Yoshikawa's Next Challenge in 2011 (Fig. 2).

In the 1980s, our group started the research by using the animal model for clarifying the participation of free radicals in the gastrointestinal mucosal injury associated with inflammation. Especially, we have succeeded in establishing a model of acute gastric mucosal injury by ischemia-reperfusion, and have demonstrated the protective effects of anti-oxidative enzymes and several anti-oxidants. Following to discussion with Prof. Helmut Sies at the meeting, the new information of the selenium-containing drug Ebselen which inhibits lipid peroxidation, we have reported the beneficial effects of Ebselen on reperfusion-induced mucosal injury in rats. Furthermore, in a process to clarify the role of nitric oxide (NO) and related gaseous mediators, Prof. Helmut Sies has provided us several crucial suggestions, leading our recent investigation about biological role of gaseous mediators including carbon monoxide (CO), not only nitric oxide.

For this special issue of Archives of Biochemisty and Biophysics in commemoration of the retirement of Prof. Helmut Sies from this journal, we indicate our recent research and the latest results of carbon monoxide and future development. If it will be one of attractive articles for him, it will be our great pleasure.

2. Potent therapeutic effects of CO on gastrointestinal inflammation

It has been proposed that genetic, immunologic, and environmental factors, including the microbiota, are involved in the initiation and perpetuation of chronic intestinal inflammation. In particular, imbalance in gut bacterial constituents provokes host

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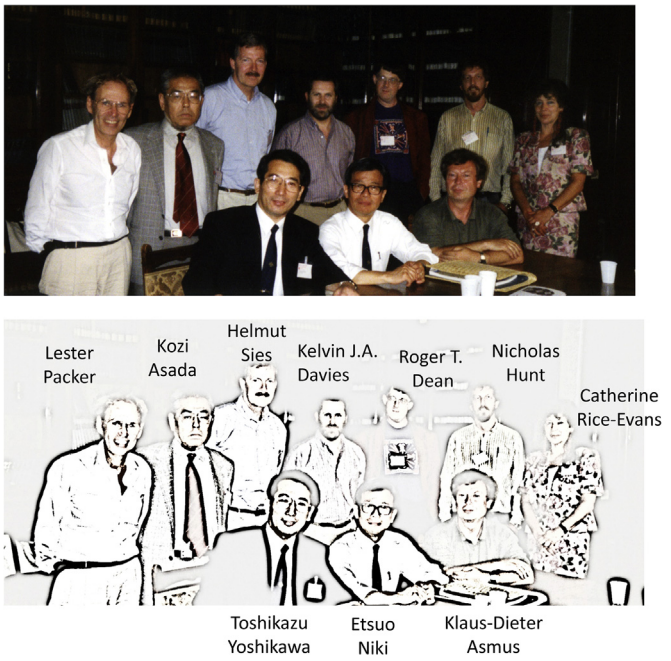

Fig. 1. International committee meeting of SFRR International at Torino in 1992.

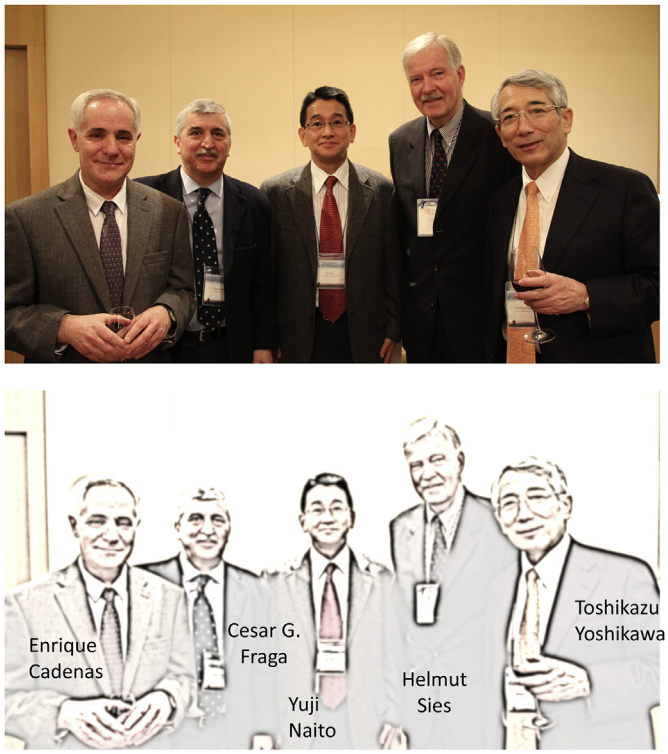

Fig. 2. International Symposium on Free Radical Research: contribution to Medicine in Celebration of Prof. Toshikazu Yoshikawa's Next Challenge at Kyoto in 2011 (Jan 20, 2011).

pro-inflammatory responses causing diseases such as inflammatory bowel disease (IBD) [1]. In addition to inflammatory reaction, mucosal healing is an important treatment end-point in IBD, and achieving mucosal healing was demonstrated to improve disease-related outcomes [2]. Biological agents targeting tumor necrosis factor-α (TNF-α) have changed the perspective of treating IBD that is refractory to standard medications and allowed the achievement of new therapeutic goals such as mucosal healing and deep remission [3]. However, some patients with IBD do not respond or respond partially to these treatments. Therefore, it is important to investigate new anti-inflammatory strategies.

CO is widely known as a toxic gas because it avidly binds to hemoglobin with a higher affinity than oxygen and forms carboxyhemoglobin, resulting in interference with the oxygen-carrying capacity of the blood and consequently tissue hypoxia. However, the potent therapeutic effects of CO have been demonstrated in experimental models of several disorders, including hypoxia [4], ischemia-reperfusion injury [5], intestinal dysmotility [6], autoimmune disease [7,8], lipopolysaccharide (LPS)-induced sepsis [9], and chronic inflammation [10], supporting the new paradigm that, at low concentrations, CO functions as a signaling molecule that exerts significant cytoprotection and anti-inflammatory effects [11]. Additionally, many reports have demonstrated that CO gas or CO-releasing molecules (CORMs) can mediate potent anti-inflammatory effects *in vivo* in colitis models [12–14]. Hence, CO can serve as an interesting potential therapeutic molecule for human IBD, with its pleiotropic anti-inflammatory effects [15]. This article provides a short review of the recent advances concerning the molecular and immunological actions of CO for intestinal inflammation as well as homeostasis, and about the potential target cells of CO.

3. CO enhances colonic epithelial restitution via FGF15 derived from myofibroblasts

It has been reported that colonic epithelial cell restitution involves complex interactions between epithelial cells, other cells within the lamina propria, and components of the extracellular matrix. In our study, a wound healing assay was also performed to evaluate the role of myofibroblasts in the process of epithelial restitution The Young Adult Mouse Colon (YAMC) cell line, a generous gift of Dr. R. Whitehead (Vanderbilt University, Nashville, TN), was used as the source of mouse colonic epithelial cells. To investigate the effect of CORM-2 on myofibroblasts related to YAMC restitution, CORM-2-treated-VUPF (Vanderbilt University Pericryptal Fibroblast) myofibroblast conditioned medium was used for a wound healing assay for YAMC monolayers. Previous studies have shown that TGF-β derived from subepithelial colonic myofibroblasts could enhance the restitution of intestinal IEC-6 and T84 cell lines. In our study, TGF-β mRNA expression in myofibroblasts was not affected by CORM-2 treatment. Although CORM-2 did not increase TGF-β expression in myofibroblasts, conditioned medium obtained from CORM-2-treated myofibroblasts could enhance epithelial cell restitution compared to that seen in ruthenium-treated myofibroblast conditioned medium used as a control [16]. To determine some factors that enhanced epithelial cell restitution in CORM-2-treated myofibroblasts conditioned medium, we performed microRNA array analysis, which indicated that CORM-2 significantly down-regulated miR-710 expression in myofibroblasts. A public web-based registry, the “miRBase” database, suggested that one of the target genes of miR-710 is fibroblast growth factor 15 (FGF15). The mRNA and protein expression levels of FGF15 in VUPF cells were enhanced by treatment with 10 μM CORM-2 [16].

In order to determine if myofibroblast-derived FGF15 is involved in epithelial cell restitution, FGF15 expression in myofibroblasts was silenced using siRNA. The conditioned medium from FGF15-silenced myofibroblasts treated with CORM-2 canceled the enhancement of epithelial cell restitution by CORM-2, suggesting that this effect was mediated by FGF15 (Fig. 3) [16]. The fibroblast growth factor (FGF) family of signaling molecules plays important roles in development, angiogenesis, and cancer. However, little is known about the identity of the cells that secrete FGF15 and the roles of FGF15 in colonic epithelial cells. In this study, for the first