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Review Article

Reactive oxygen species, nutrition, hypoxia and diseases: Problems solved?

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ABSTRACT

Within the last twenty years the view on reactive oxygen species (ROS) has changed; they are no longer only considered to be harmful but also necessary for cellular communication and homeostasis in different organisms ranging from bacteria to mammals. In the latter, ROS were shown to modulate diverse physiological processes including the regulation of growth factor signaling, the hypoxic response, inflammation and the immune response. During the last 60–100 years the life style, at least in the Western world, has changed enormously. This became obvious with an increase in caloric intake, decreased energy expenditure as well as the appearance of alcoholism and smoking; These changes were shown to contribute to generation of ROS which are, at least in part, associated with the occurrence of several chronic diseases like adiposity, atherosclerosis, type II diabetes, and cancer. In this review we discuss aspects and problems on the role of intracellular ROS formation and nutrition with the link to diseases and their problematic therapeutical issues.

Contents

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1. Introduction

The research within the last twenty years on chemically reactive molecules containing oxygen, commonly called reactive oxygen species (ROS), has shown that these molecules are important for cellular communication and homeostasis in different organisms ranging from bacteria to mammals. Thereby, ROS were shown to modulate diverse physiological processes including the regulation of growth factor signaling, the hypoxic response, inflammation and the immune response in mammalian cells. ROS are often simply called "free radicals" because their majority is characterized by at least one unpaired electron in their outer orbitals; however, peroxides like hydrogen peroxide may also give rise to the formation of oxygen radicals and are therefore also considered as ROS. Frequently the incomplete reduction of oxygen by one electron producing superoxide anion ($O_2^{\cdot-}$) is the first step for the formation of most other ROS [1,2].

The action of ROS is usually balanced by the antioxidative capacity of a cell or organism and a disturbance of this balance in favor of a prooxidant state is commonly referred to as oxidative stress. Oxidative stress is usually coupled to harmful effects due to the primary chemical reactions of ROS with lipids and proteins. In this respect, diseases frequently associated with a Western lifestyle and nutritional regime like type II diabetes, cardiovascular diseases or cancer were found to be associated with a deregulated ROS formation [3–7]. Hence, it appears to be of special interest that production of ROS due to nutrition may affect signaling pathways and the pathogenesis of these diseases. In the current review we aim to summarize some aspects on the role of ROS, nutrition, intracellular ROS formation, and the link to diseases.

2. Cellular sources of ROS

A number of studies within the last decade indicated that overnutrition-induced ROS formation and oxidative stress contribute to the development of metabolic disorders, in particular to insulin resistance, as well as to cardiovascular diseases, and cancer [8–12].

In mammalian cells ROS can be generated in different cellular compartments such as membranes, cytoplasm, mitochondria, endoplasmic reticulum (ER), lysosomes, and peroxisomes (Fig.1). In the following we will give only a short summary because the role of each compartment in ROS formation has been discussed elsewhere in excellent detail [13].

2.1. Plasma membranes and ROS production

The prototypic NADPH oxidase was found in phagocytes localized in the plasma membrane and phagosomes [14]. It is composed of gp91phox and the smaller subunit p22phox forming the flavocytochrome b558 [15,16] which is the catalytic core of the NADPH oxidase generating $O_2^{\cdot-}$. Several homologs of gp91phox – now termed NOX2-named NOX1-5, and the more distantly related DUOX1/2 (dual oxidases) were found [17–19]. NOX2 is mainly expressed in polymorphonuclear cells, macrophages and endothelial cells, but its expression was also verified in other cell types including cells from the CNS, smooth muscle cells, fibroblasts, cardiomyocytes, skeletal muscle, hepatocytes, and hematopoietic stem cells [20] (Table 1).

NOX1 is highly expressed in the colon epithelia [21] and was also detected in lower abundance in smooth muscle cells, endothelial cells, uterus, placenta, pancreatic islet beta cells and other cell types [22,23]; it is mainly localized in the plasma membrane of caveolae, but also in early endosomes or nucleus [24,25].

NOX3 has long been considered to be expressed in fetal tissues, but is it now also found in the inner ear, HepG2 cells, the mouse macrophage cell line RAW264.7, and in murine lung endothelium [26] (Table 1).

NOX4 is widely expressed in many tissues, especially in the kidney [27], but also in most other tissues and cells including endothelial cells, smooth muscle cells, fibroblasts and hepatocytes [25,28–30]. In contrast to most other NOXes, NOX4 is mainly localized in the endoplasmic reticulum as well as in the outer membrane of the nucleus [31,32]. Finally, NOX5 expression has been detected in testis, prostate, spleen, lymph nodes, but also in endothelial and smooth muscle cells [26] and its mainly localized in the endoplasmic reticulum of the cell [33] (Table 1).

The two DUOX1/2 proteins are highly expressed in the thyroid, but also in lung epithelium and gastrointestinal tract [34–36]; mainly in the endoplasmic reticulum and plasma membrane [32].

Most NOXes as well as the two DUOX members require cytosolic subunits for full activation. In the case of NOX2 these are the cytosolic subunits p40phox, p47phox, p67phox as well as the small monomeric GTPase Rac [16]. NOX1 and NOX3 can be regulated by NOXO1 (p67phox homolog) and NOXA1 (p47phox

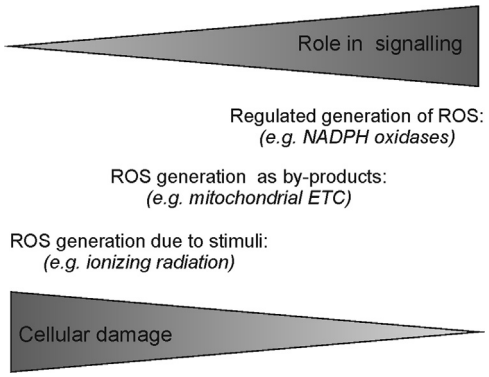

Fig. 1. ROS generation in cells. ROS can be generated in response to various stimuli among them diets or radiation which is supported by the action(s) of enzyme (s) located in different intracellular compartments. ETC, electron transport chain;