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Mini-review

Peroxiredoxins, a novel target in cancer radiotherapy

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ABSTRACT

Reactive oxygen species (ROS) are toxic at high levels in the mammalian cells. Mammalian cells have developed many enzymatic and nonenzymatic antioxidative systems in various cellular compartments to maintain an appropriate level of ROS and regulate their action. Peroxiredoxins (Prxs), a family of peroxidase that reduced intracellular peroxides (one type of ROS) with the thioredoxin system as the electron donor, were highly expressed in various cellular compartments. In this minireview, we discussed the regulation of Prxs expression in cancer cell and its relationship with ionizing radiation. As Prxs could be induced by radiation and its expression status could determine the radiosensitivity of cancer cells, Prxs might be a potential target for radiotherapy in cancer.

1. Introduction

Reactive oxygen species (ROS) are toxic at high levels in the mammalian cells, which can be derived from physical or chemical stimulus. Peroxides belong to ROS and H_2O_2 is one of the peroxides. They are usually more reactive than the corresponding non-radicals because they can act as oxidizing agents. Endogenous ROS are usually by-products of cellular metabolism, and can be induced to high level. Though ROS cause cellular damages, recent studies found H_2O_2 signaling is associated with the signal transduction of growth factors such as epidermal growth factor (EGF) and platelet-derived growth factor (PDGF), and required for subsequent protein tyrosine phosphorylation. This indicated cellular H_2O_2 might be a new kind of messenger and is stringently controlled in mammalian cells [1]. ROS are conventionally considered to have carcinogenic potential and to promote invasiveness. In order to maintain an appropriate level of ROS and regulate their action, mammalian cells have developed many enzymatic and nonenzymatic antioxidative systems in various cellular compartments. The enzymatic systems include catalase, superoxide dismutase, and glutathione-dependent peroxidase, and the recently characterized peroxiredoxins (Prxs). The presence of all these enzymes creates a complex network of peroxidases. Prxs, a well-defined family of highly conserved antioxidant enzymes, has been discovered and shown to play an important role in peroxide detoxification [2,3].

The important physical stimulus that causes ROS is ionizing radiation (IR). IR is one of the main treatment modalities used in the management of cancer, and it can evoke a series of biochemical events inside of the cell. These events include many important cellular processes, such as DNA damage and repair, apoptosis, cell cycle control, signal transduction, and oxidative stress response [4,5]. IR can act directly and indirectly. The direct effect includes damage of DNA and proteins by the energy of radiation and by the reactive oxygen species (ROS) derived from intercellular water. The indirect effect is the secondary response involved in signal transduction and gene expression. Among these effects, ROS induced by IR is crucial for cell survival. The mechanisms of ROS induced by IR involved in cell death especially in the induction of apoptotic death, which

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were widely investigated in the field of cancer radiotherapy. The deleterious effects by ROS include DNA damage and membrane oxidative damage. The formation of single and/or double stranded breaks of DNA resulted in cell cycle arrest and recruitment of DNA repair enzymes to rescue cells from the damage. Mammalian cells have developed complicated antioxidant systems to deal with the oxidative stress. In this minireview, we will focus on the regulation of Prxs and its potentiality as a target of radiotherapy in cancer.

2. Molecular biology of Prxs

2.1. Genomic structures

The first member of this family was discovered as a 27-kDa protein in yeast [6]. Different from catalase, glutathione peroxidase, superoxide dismutase, or iron chelation activities, its protection activity was specific for mixed-function oxidation systems containing thiols, and its expression was induced by oxidative stress. Since then, Prxs have been identified in many organisms and constitute a ubiquitous family of thiol-dependent peroxidases catalyzing the reduction of hydrogen peroxide. This family of antioxidant enzyme is highly conserved throughout evolution and widely distributed among bacteria and eukaryotes [7]. Compared with other antioxidant enzymes, Prxs have particular mechanism of peroxide detoxification with reducing equivalents provided through the thioredoxin system but not from glutaredoxin. Redox-active conserved cysteine of Prxs is oxidized to sulfenic acids by peroxide substrates, consequently inactivating their peroxidase enzyme activity. However, recent finding demonstrated that the oxidized sulfenic acid could be converted back into a thiol in a second reduction step [2]. Six Prxs isoforms were found in mammalian cells, but they are nonredundant antioxidant proteins. Each member contains a conserved cysteine residue in the N-terminal region that is the active site of catalysis. Based on its conserved cysteine residues and their catalytic mechanisms, mammalian Prxs can be divided into three subgroup, namely typical 2-Cys, atypical 2-Cys, and 1-Cys Prxs. Prx-I–IV belong to typical 2-Cys and Prx-V belongs to atypical 2-Cys group, within which all members contain two conserved cysteine residues. And Prx-VI belongs to 1-Cys Prxs subgroup in which one cysteine residue is conserved. Moreover, another subgroup named Prx-Q was extensively found in plants, which also contains two cysteine residues [8].

The six isoforms of human Prxs were located on chromosome 1,4,8,19 and X, with Prx-III and V on the same chromosome 19. All members consist of five exons at least and Prx-III and IV had maximum seven exons. The four members of 2-Cys subgroup showed high similarity, indicated that they evolutionally derived from same ancestor gene. However, the similarity between subgroups is much lower. Many pseudogenes of each member of Prxs were found in the genome of mouse and human. These pseudogenes showed structural characters such as loss of intron, flanking with terminal repeat, which suggested that they might be retroposons.

2.2. Gene expression

Prxs are expressed at high levels in organisms. They are among the most abundant proteins in *Escherichia* coli and constitute 0.1–0.8% of soluble proteins in mammalian cells [9]. This suggested Prxs could be classified as housekeeping genes. In mammalian cells, different cellular distribution of each member was found. Prx-I, II and VI were located in cytosol. Prx-III is exclusively localized to mitochondria. Prx IV is synthesized with an NH_2-terminal signal sequence for secretion and is present in the endoplasmic reticulum as well as in the extracellular space [10]. Prx-V is expressed in different forms more widely distributed within mammalian cells as it has been found in the cytosol, mitochondria, peroxisomes and in the nucleus [11].

Although known as housekeeping genes, the expression of Prxs is inducible by various stimuli. The induction of Prxs by oxidative stress including O^2, Fe^{3+}, or 2-mercaptoethanol was found early after the discovery of the first member in yeast. This induction represented an adaptive response that evolved to protect cells against damage. However, heat shock did not cause any significant increase. Since then, the induction of Prxs by oxidative stress was widely studied, and each member could respond immediately by treatment with H_2O_2 [12,13]. Besides H_2O_2, other chemical such as okadaic acid (OA), TPA and butylated hydroxyanisole could also induce the expression of Prx-I [14–16]. On other hand, increased expression of Prxs contributed to more resistance to oxidative stress. Another important stressor was ionizing radiation, which also induced the expression of Prxs (see below). The expression of Prxs under physiological and pathological status has been widely investigated. At present, Prxs are functionally versatile. Besides their cytoprotective antioxidant function, Prxs appeared to play a role in cell proliferation, differentiation, immune response, protection of oxidant-sensitive proteins, regulation of cellular H_2O_2 and control of apoptosis, processes involving a redox signaling (Review [17]). Another important finding is that aberrant regulation of Prxs has been discovered in various cancers.

3. Aberrant regulations of Prxs in cancer

The process of transformation and tumorigenesis is accompanied by cumulative mutations in genetic pathways that confer a growth advantage of cancer. So this process is thought to be involved with many genes (e.g. oncogenes and tumor suppressors) and is a result of multistage of mutagenesis. The most outstanding biochemical function of Prxs is to reduce peroxide. Oxidative stress and damage by free radicals have been showed involved in tumorigenesis. ROS is conventionally considered to have carcinogenic potential and to promote invasiveness. Recent studies indicated cellular H_2O_2 might be a new kind of messenger and is stringently controlled in mammalian cells [18]. Prxs expression was inducible by oxidative stress, which indicated that Prxs activity might be associated with formation of ROS, and might be importance factors of tumorigenesis. Many studies indicated that