Manganese superoxide dismutase in carcinogenesis: friend or foe?

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Abstract

Superoxide and its derived ROS (reactive oxygen species) have been considered for a long time to be generated as toxic by-products of metabolic events. Although ROS generated in low amounts are able to act as signalling molecules, ROS appear to also play a major role in aging and in the pathogenesis of diseases such as inflammation, diabetes and cancer. Since superoxide formation, in particular in mitochondria, is often considered to be an initial step in the pathogenesis of these diseases, improper function of the MnSOD (mitochondrial superoxide dismutase; SOD2) may be critical for tissue homoeostasis. However, the underlying regulatory mechanisms appear to be multiple and this article summarizes current aspects by which MnSOD can regulate carcinogenesis under various conditions.

Introduction

Apart from being a substrate in various enzyme reactions, oxygen appears to be also the universal electron acceptor in electron transfer processes occurring in various aerobic living species. During these events some of the O_2 consumed is converted into ROS (reactive oxygen species), the vast majority of which are produced in mitochondria as unwanted by-products during the combustion of nutrients [1]. Superoxide ($O_2^{\bullet -}$), formed by a one electron reduction of O_2, is often the initial step in ROS generation and serves as a precursor for the generation of other ROS such as H_2O_2, hydroxyl radicals ($^{\bullet}OH$), peroxynitrite ($ONOO^-$), HOCl (hypochlorous acid) and singlet oxygen ($^1O_2$) [1].

Although research during the last decades has shown that ROS generated in lower concentrations can act as messengers in signal transduction pathways modulating gene expression in a variety of cell types and under several biological conditions, superoxide and other ROS are primarily known to be highly cytotoxic [1]. They can cause damage to macromolecules such as lipids, DNA and proteins and play a major role in the pathogenesis of a number of diseases, including inflammatory disease, diabetes, cancer, neurodegenerative diseases and other ageing-related diseases [1]. To avoid damage, cells have evolved several lines of defence mechanisms, which include non-enzymatic molecules, and enzymes that dismutate $O_2^{\bullet -}$ into H_2O_2 [SODs (superoxide dismutases)] or degrade H_2O_2 (catalase, glutathione peroxidases and peroxiredoxins). Since superoxide formation, in particular in mitochondria, is often considered to be a crucial process for the pathogenesis of the above-mentioned diseases, improper function of the mitochondrial SOD may be critical for tissue homoeostasis [2]. In the following, we will therefore summarize some aspects showing the importance of MnSOD (manganese superoxide dismutase) in tissue homoeostasis and carcinogenesis.

Key words: inflammation, liver failure, manganese superoxide dismutase, mitochondrion, reactive oxygen species.

Abbreviations: HIF, hypoxia-inducible factor; MMP, mitochondrial membrane potential; MnSOD, manganese superoxide dismutase; PHD, prolyl hydroxylase; PKB, protein kinase B; PKC, protein kinase C; ROS, reactive oxygen species; SOD, superoxide dismutase.

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SODs: common aspects

SODs are a family of metalloenzymes of which three isoenzymes are known in mammals. They all catalyse the dismutation of $O_2^{\bullet -}$ to H_2O_2 and O_2 at a near diffusion limited rate [3].

The Cu/Zn–SOD, or SOD1, is mainly found in the cytosol [4], although small amounts have been reported to be found also in the intermembrane space of mitochondria [5] as well as in the nucleus [6].

The MnSOD resides predominantly in the mitochondrial matrix; the protein is encoded by the *SOD2* gene and forms a homotetramer with one manganese ion per subunit. MnSOD was found also in nucleoid complexes with mtDNA [7] to protect mtDNA and mtDNA polymerase c from $O_2^{\bullet -}$-mediated damage and inactivation respectively. Interestingly, MnSOD appears to be subject to inactivation due to ROS-mediated oxidation, and tyrosine nitration [8,9].

A third form is EC-SOD, or SOD3, which is a copper- and zinc-containing enzyme found extracellularly either anchored to sulfated GAGs (glycosaminoglycans) or circulating in plasma and other fluids [10]. The extracellular SOD is likely to play a particularly important role in protecting the endothelium [11].

MnSOD in tumours

Alterations in the levels of proteins involved in redox regulation have been reported in a number of tumour types. Generally, antioxidant defence enzymes are decreased in

tumour tissue when compared with normal tissue [12,13]. First evidence that MnSOD deficiency contributes to tumorigenesis came from studies showing a reduction of MnSOD in various types of tumours [14–16]. In human oral cancers, a high expression level of MnSOD was associated with better disease-specific survival, especially for patients with moderate or poor cell differentiation, and early stage buccal mucosal squamous cell carcinomas [17]. In human oesophageal cancers, studies have shown that decreased MnSOD levels are associated with increased incidences of oesophageal adenocarcinoma [18]. Moreover, when analysing 240 patients with diffuse large B-cell lymphoma it was found that patients with the worst prognosis had decreased expression of MnSOD, but also catalase, glutathione peroxidase and vitamin D_3 up-regulated protein 1 [19]. Likewise, heterozygous MnSOD-knockout mice and hepatocyte-deficient MnSOD-knockout mice showed an increase incidence of tumours [20]. By contrast, a higher expression of MnSOD was found in cancerous than in non-cancerous tissues, where higher MnSOD levels were found in thyroid [21], brain [16], oesophageal, gastric [22] and colorectal [23] cancers, which leads to the question whether the MnSOD increase is indeed beneficial or a reaction of the cells to fight the tumour.

In addition, MnSOD exists in at least two functional variants in humans [24]. These variants which show either reduced mitochondrial translocation or enzyme activity [25] were associated with a higher incidence in human cancer [26,27].

Overall, the majority of the findings strongly support the role of MnSOD as tumour suppressor as well as the role of oxidative stress as tumour promoter.

MnSOD affects cell migration, invasion and proliferation

Migration and invasion are characteristic for tumour cells and an enhanced migration and invasion is usually associated with a more metastasizing phenotype. MnSOD appeared to decrease migration of VSMCs (vascular smooth muscle cells) during neointima formation after balloon injury in mice, whereas knockdown of MnSOD increased smooth muscle cell migration [28]. In contrast with these findings are reports indicating that a high MnSOD expression promotes migration and thus a malignant phenotype of HT-1080 fibrosarcomas [29]. Furthermore, knockdown of MnSOD in a highly metastatic tongue squamous cell carcinoma model by RNAi caused a significant reduction of migration and invasion [30].

Thus these findings indicate that cell migration is a complex process involving many molecular interactions and as such the effect of MnSOD on migration might in part be tissue specific.

Changes towards a more malignant phenotype due to the loss of MnSOD expression are also reflected in cell proliferation. Heterozygous MnSOD-knockout mice showed an increased rate of proliferation [31] and suppression of MnSOD by siRNA resulted in stimulation of proliferation in ovarian cancer cells [32]. Furthermore, overexpression of MnSOD has been shown to inhibit cellular proliferation of numerous tumour cell types both *in vitro* and *in vivo* [28,33,34]. These findings are in line with studies showing low MnSOD levels during the S-phase of the cell cycle [35] and with observations showing a reversed transformation upon overexpression of MnSOD in different cancer cell lines [36,37].

In addition, MnSOD increased during progression from early stage benign tumours to late stage malignant ones in a DMBA/TPA multistage skin carcinogenesis model [38]. These data together with the finding that overexpression of MnSOD prevented cell growth and reversed tumorigenesis [36,37,39] indicate that the observed increase in MnSOD levels in advanced carcinomas is a consequence of the defence rather than the cause.

MnSOD contributes to mitochondrial integrity and oxidative phosphorylation

The scavenging action of MnSOD seems to play a critical role in maintaining the integrity of mitochondria. The loss of MnSOD would be expected to impair the proper removal of superoxide within mitochondria and cause an overall increase in mitochondrial ROS levels and a change in the MMP (mitochondrial membrane potential). Indeed, the MMP was found to be reduced in MnSOD depleted cells [40].

Furthermore, increased energy production by glycolysis, without a corresponding increase in oxidative phosphorylation, is another well-documented feature of cancer and corresponds well with an indication of mitochondrial damage caused by loss of MnSOD. Indeed, ATP production by oxidative phosphorylation was shown to be impaired in heterozygous MnSOD-knockout mice [41], whereas overexpression of MnSOD in fibrosarcoma cells increased ATP generation during oxidative phosphorylation [42]. This is also associated with defects in lipid metabolism where postnatal lethal $Mnsod^{-/-}$ mice exhibited lipid accumulation in their liver and where $Sod2^{+/-}$ mice also displayed disrupted mitochondria, accumulation of lipid droplets and increased lipid peroxidation [43].

Overall, these findings show that loss of MnSOD alters mitochondrial integrity and oxidative phosphorylation.

MnSOD modulates expression and activity of some key regulatory proteins

ROS generation, as by-products or as signalling molecules, is influenced by developmental aspects, tissue-specific features and environmental factors. One such important factor with respect to tumorigenesis appears to be tumour hypoxia which persists in almost all solid tumours, and the ability of cells to survive under low O_2 conditions is a key feature of malignant tumours [44]. Hypoxia has been found to be an inducer

of cellular stress and MnSOD has been shown previously to be able to protect cells against oxidative stress induced by reoxygenation after hypoxia [40,45]. Thus it appeared that MnSOD had an impact on the key regulatory HIF-1α (hypoxia-inducible factor 1α). Indeed, overexpression of MnSOD in human breast carcinoma MCF-7 cells modulated the appearance of HIF-1α in a biphasic manner: low level expression of MnSOD (2–6-fold) reduced the hypoxia-dependent induction of HIF-1α, whereas a more than 6-fold increase in MnSOD activity restored the hypoxia-dependent induction of HIF-1α [46]. These observations are in line with the regulatory mechanism of HIFα degradation. Degradation of HIFα is known to require the presence of Fe^{2+} as a cofactor for the PHDs (prolyl hydroxylases), which hydroxylate HIFα at conserved proline residues, mediating proteasomal degradation [46]. Whereas $O_2^{\bullet -}$ in general causes reduction of iron, H_2O_2 oxidizes it to Fe^{3+}. Thus overexpression of MnSOD and accumulation of H_2O_2 would decrease PHD activity and HIFα degradation, whereas the loss of MnSOD and accumulation of $O_2^{\bullet -}$ should increase PHD activity and HIFα degradation. However, these findings are contrasted by a study showing that SOD mimetics suppressed angiogenesis via inhibiting HIF-1α and the expression of its target gene VEGF (vascular endothelial growth factor) in a mouse model of breast cancer [47].

Furthermore, MnSOD may not only influence HIF-1α since it was also found that MnSOD overexpression increased or decreased the activity of the transcription factor AP-1 [31,48]. Another transcription factor which appears to interfere with MnSOD via direct interaction is p53. To achieve this interaction, p53 is transported to the mitochondria before it is translocated to the nucleus. In the mitochondria p53 physically interacts with MnSOD and inhibits its enzymatic activity and thus contributes to enhanced ROS generation [49].

Apart from transcription factors, MnSOD also appears to affect major signalling components such as PKB (protein kinase B, also known as Akt), which is in general associated with cellular transformation as well as migration and inhibition of apoptosis. Recent data showing decreased PKB phosphorylation in MEFs (mouse embryonic fibroblasts) from *Mnsod*$^{-/-}$ mice [45] and data from lymphoma cells where increased MnSOD expression or treatment with manganese porphyrin potentiates dexamethasone-induced apoptosis support the view that MnSOD contributes to apoptosis [50]. In addition, MnSOD overexpression also suppressed the activation of PKCε (protein kinase Cε), a PKC isoform activated by tumour promoting phorbol esters [48].

Together, it becomes obvious that the type of tissue, the developmental stage at which transcriptional events occur, and environmental factors may affect tumorigenesis.

Conclusion

A variety of studies demonstrated that MnSOD plays a critical role in tumorigenesis and is associated with signalling, transcriptional regulation, mitochondrial metabolism and energy homoeostasis. Although decreases in ROS formation via MnSOD expression/activity were shown to improve mitochondrial integrity and to reverse the glycolytic switch in various cancer cells, other downstream regulators such as p53, aberrant acetylation by Sirt3 and epigenetic modifiers as well as environmental changes may contribute to cellular damage creating a tumour-permissive phenotype. These multiple layers of regulation contribute certainly to the many caveats and limitations that it is crucial to consider when interpreting data from reports indicating a tumour-suppressive role of MnSOD, and others describing a higher expression of MnSOD in some cancers. Thus the question of whether MnSOD is friend or foe in cancer remains, but future studies evaluating genome-wide alterations following antioxidant induction can help to explore the role of MnSOD not only in cancer, but also in other diseases, more efficiently.

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