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Commentary

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To Manganese Porphyrins, A Double-Edged Sword to Either Combat or Provoke Oxidative Stress, and Their Specific Potential

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Commentary

Dear Editor,

We wish to provide our opinion as another piece to a complex redox biology mosaic. In fact, we intended to stress the notion of multivalent potential of cationic manganese porphyrins (Mn(III)-Ps) regarding the *in vitro* and *in vivo* generation of Reactive Oxygen Species (ROS). Depending on their structure, distinct MnPs may actually exert opposing effects, either pro-oxidative or anti-oxidative; and, these distinct properties have been suggested for specific therapeutic use **[1].** In this connection, there are two particular aspects of redox biology we would like to mentioned here.

First, there is remaining controversy in understanding ROS in biological systems, utmost as detrimental **[2-6]** or beneficial **[6-12]** agents. Even though both the ROS production and their elimination are tightly controlled by enzymatic and non-enzymatic mechanisms hence enabling ROS to be involved in cellular signaling, many researchers in the field understand the concept of oxidative stress, i.e. the prevalence of prooxidative processes and ROS overproduction, to be a pathological event **[13-15].** On the other hand, a number of rigorous clinical trials failed to provide sufficient evidence to this concept, in term of the effective treatment of pathologies involving oxidative stress by exogenous antioxidants **[16].** Indicative, these failures may be explained when accepting a beneficial role of ROS in maintaining cellular homeostasis and hence the health of the cell; the observed complications of the

conditions intended to get better with administering exogenous antioxidants might simply result from the unintended inhibition of ROS mediated cellular functions. In this regard, the critical role of ROS in the process of eliminating aberrant cells including cancer cells physiologically by native immune system has been indicated; also, under their therapeutic eradication by radiological and chemotherapeutic procedures, the ROS-mediated destruction of the cancer cells is involved **[10,11].** As another example in favor of ROS beneficial role, the mechanism underlying the turnover ($t_{1/2}$ = 12 h) of high molecular mass (h.m.m.) Hyaluronic Acid (HA) within the synovial fluid with no hyaluronidase activity by means of ROS-mediated oxidative degradation of h.m.m. HA with ROS themselves originated from not fully competent chondrocyte mitochondria was hypothesized **[17];** and, the resulting HA fragments were indicated to stimulate a subsequent synthesis of new h.m.m. HA molecules by HA synthase in beta-synoviocytes **[18].**

Second, process of redox cycling of transition metal within the coordination center of the octahedral structure of Metalloporphyrins (MePs) is responsible for their oxidative-reductive activity. Originally studied as antioxidants, MePs found to readily decompose superoxide anion radicals have been studied as effective Superoxide Dismutase (SOD) mimetics **[19].** Based on their effectiveness, smaller size, longer half-life, and similarity in function of the SOD enzyme, MePs began to represent a significant interest in treating oxidative stress **[20].** Aromatic ring structure is fundamental for good lipid solubility and cell permeability of the entire porphyrin complex **[21],** and the cationic MePs with manganese, iron, copper and zinc in their coordination center were extensively studied. As for their therapeutic potential, manganese-based SOD mimetics overcome other metal counterparts due to lower toxicity, higher catalytic activity, and increased stability *in vivo* **[22].** MnPs have actually shown high antioxidant and anti-inflammatory effects in a vast disease models, including stroke, cancer, diabetes, ischemia-reperfusion, and radiation injury **[23].** Structure modifications to reduce MnPs toxicity while keeping their lipophilicity and SOD-mimetic activity were performed; hydrophilic analogues (e.g. MnTE-2-PyP^{5+} and MnTDE-2-mP^{5+}) were found effective in animal models, while lipophilic analogues (e.g. MnTnHex-2-PyP^{5+}) were proposed to cross blood brain barrier and target the central nervous system and mitochondria within. More recently, a number of MnPs effectively targeting cellular redox environment have reached sufficient maturity for clinical applications and have been subjected to testing in several clinical trials. E.g., their applications have been tested for psoriasis and atopic dermatitis by MnTE-2-PyP^{5+} (BMX-010) **[24];** and glioma (phase III), rectal cancer (phase II) and anal cancer, brain metastases, head and neck cancer (phase I/II) by MnTnBuOE-2-PyP^{5+} (BMX-001) **[25].** Moreover, their help in support of cancer therapy with radiation and chemotherapy while protecting of normal tissue has been indicated **[26].** Intriguingly, some Mn(III)-Ps were found to generate ROS hence inducing oxidative stress, and their new therapeutic applications were indicated, specifically for anticancer treatment **[11,27-30].** The mechanism of peroxidative degradation of h.m.m. HA induced by ROS produced via redox cycling of MnPs with ascorbate and cupric ions has been suggested; the HA layer covering cancer cells may thus undergo destruction enabling the cancer cells being exposed to innate immune system and effectively fought out.

Hence, based on their ability to modulate oxidative status *in vivo*, by ROS generation or its inhibition, particular MnPs may be advanced for research studies aiming at (i) elucidating a true role of ROS and oxidative stress in cellular biochemistry, and (ii) revealing effective ways of regulating redox processes the desired way.

Concluding, the metal center of cationic Mn(III)-Ps easily accepts and donates electrons as illustrated in the reaction of superoxide dismutation. MnPs may thus be equally good as antioxidants or prooxidants, and as such may be applied to readily modulate cellular redox status using their specific potential. Intricacy of biological redox systems and multivalent redox chemistry of MnPs *in vivo* are under continuing research effort. Better understanding the role of ROS in normal and pathobiochemical events in the cell are needed to influence its redox processes in favor of the cellular health and also to treat properly the diseases involving oxidative stress, whether being the detrimental or beneficial event.

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