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EDITORIAL

# Special collection: Nitric oxide in cancer ☆

Nitric oxide (NO) is a lipophilic, highly diffusible, and short-lived physiological messenger. NO is synthesized by three different gene-encoded NO synthases (NOS) in mammals: neuronal NOS (nNOS or NOS-1), inducible NOS (iNOS or NOS-2) and endothelial NOS (eNOS or NOS-3). NO regulates a variety of important physiological responses, including vasodilation, respiration, cell migration, immune response and apoptosis. All these features are relevant in cancer in which the key hallmarks are unlimited replicative potential, insensitivity to growth-inhibitory signals, evasion of apoptosis, cellular stress, sustained angiogenesis, invasiveness and metastatic potential. The present special issue entitled "Nitric oxide in cancer" derives from the IV International Workshop on "Nitric oxide in cancer" held in the Institute of Biomedicine of Sevilla (IBiS) (March 13–14, 2015). The program included six sessions that were focused on "Nitric oxide, mutagenesis, carcinogenesis, tumor promotion and tumor growth", "Nitric oxide regulation of cell death pathways", "Nitric oxide: proliferation and epithelial-mesenchymal transition", "Regulation of immune response by nitric oxide", "Antitumoral activity of nitric oxide-based releasing strategies: pre-clinical studies" and "Antitumoral activity of nitric oxide-based releasing strategies: clinical trials". In addition, a keynote lecture entitled "Nitric oxide and oxygen: Actions and interactions in health and disease" was delivered by Sir. Salvador Moncada. The present thematic issue "Nitric oxide in cancer" includes different original research manuscripts and review articles written by participants in the workshop and which were focused in all aspects discussed at the meeting regarding the chemical reactivity of NO, its role in cell proliferation/death and metabolism of tumor cells, as well as NO-based antitumor activity or preventing the side effect of chemotherapy during the treatment of patients with cancer.

NO has been shown to regulate different pathways involved in the cell proliferation and death, as well as the epithelial-mesenchymal transition of tumor cells [1,2]. In particular, STAT3 and NF-κB are key transcription factors involved in tumor progression, chemoresistance, and metastasis in cancer. Kaliyaperumal et al. [3] demonstrated that S-nitrosylation of STAT3 and NF-κB has a beneficial effect during cisplatin and radiation-treated head and neck cancer cells. Cell death signaling and proliferation are profoundly altered by NO in tumor cells. In this sense, the intracellular sustained generation of NO from NOS-3 induced cell death and arrested cell proliferation, as well as altered cell metabolism and redox status in hepatocellular carcinoma [4]. NO reacts with superoxide anion generated at the membrane level and responsible for tumor cell survival, with the further generation of highly reactive species that promote apoptosis [5,6]. One of the key features of tumor cells is the acquisition of resistance to apoptosis. The S-nitrosylation of cell death receptors (TNF-R1, CD95 and TRAIL-DR1) stimulates the extrinsic cell death signaling [7]. In addition, the denitrosylating activity of cell death receptors and cell proliferation arrest by Sorafenib, a tyrosine kinase inhibitor for the recommended treatment of patients with advanced renal and liver cancer, promote the activation of downstream apoptotic markers in hepatoblastoma cells [8]. NO donors such as NOSH-Aspirin [9] and NOSH-Sulindac [10] have shown to exert potent COX-1 and COX-2 inhibition, and reduced cell survival in colon cancer cells. The susceptibility to induce NO production during Bacillus Calmette-Guerin administration is relevant during the treatment of patients with bladder cancer [11]. The effect of NO on increased tumor blood flow, cellular respiration, cell signaling, and on the production of reactive oxygen and nitrogen species (RONS) appear to be relevant for its activity as a radiosensitizer [12] and a photosensitizer [13]. In addition, the increased diffusion of NO through the cytoplasm and plasma membranes allows this signaling molecule to easily spread from irradiated cells to bystander cells without the involvement of gap junction intercellular communication. These NO-dependent effects include the stimulation of genomic instability (GI) and the accumulation of DNA errors in bystander cells without direct DNA damage [14]. The effectiveness of tyrosine kinase inhibitors and neutralizing antibodies against growth factors/receptors in patients with cancer are widely associated with increased hypertension which has been postulated to be related to either direct downregulation of NOS expression or the microvessel density (rarefaction). In this sense, NO donors could be successfully used not only for the treatment of developed angiogenesis-inhibitor-induced hypertension but also for preventive effects [15].

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