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Nitromedicine: a new concept

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Nitromedicine is a new medical treatment paradigm, focused on increasing nitric oxide (NO) bioavailability and modulating redox-signaling pathways combined with phototherapy, electrotherapy and stem cell therapy. It has been known since the discovery of the biological role of NO in the 1980s, that supplying NO donors such can have many beneficial effects in different conditions by stimulating stem cells and modulating the immune response, but there also exists a substantial risk of side-effects with long-term use. Excess NO can inhibit mitochondrial metabolism by binding to cytochrome c oxidase (CCO) and can also produce reactive nitrogen species (Peroxynitrite) by interacting with reactive oxygen species (ROS). To avoid these potential damaging side-effects we propose to combine the use of NO donors with three additional components. Firstly we believe that addition of antioxidants such as hydrogen sulfide donors, polyphenols and vitamins can neutralize ROS and RNS. Secondly we believe that application of appropriate wavelengths and dosages of light (blue, red or near infrared depending on the exact condition being treated) will dissociate NO from CCO (and other storage sites) thus restoring mitochondrial ATP production and stimulating healing in many situations. Thirdly delivering electrons to the body might help to saturate the free radicals with electrons, eliminate underlying oxidative stress, stabilize mitochondria, prevent further formation of pathological free radicals and increase the nitric oxide bioavailability. This combination therapy may be applied to treat a large variety of oxidative stressed related diseases such as degenerative diseases, immunological diseases, chronic infectious diseases, cancers and a broad range of unmet medical needs involving chronic inflammation with an emphasis on pain management.

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A unique network involving CXCR4 and CXCR7 coordinates cardiac lineage specification and mobilization of induced pluripotent stem cells

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An adult heart has an intrinsically limited capability to regenerate damaged myocardium. Human embryonic and induced pluripotent stem cell (hESC/hiPSC)-based therapies offer a unique strategy for developing cell replacement treatments for numerous disorders including cardiac diseases. The present study identifies a unique signaling network, SDF-1/CXCR4/CXCR7, that regulates cardiac lineage differentiation and migration in human induced pluripotent stem cells (hiPSCs). The fact that SDF-1 binds to CXCR4 and CXCR7 raises a concern on how to distinguish the potential contribution of the SDF-1/CXCR7 pathway from SDF-1/CXCR4 pathway in all the processes that were previously attributed to SDF-1/CXCR4. Therefore, we set these studies to disseminate the role of the SDF-1/CXCR4/CXCR7 network in cardiogenic lineage differentiation and migration of hiPSCs with the premise that their improved recruitment could translate into therapeutic benefits. Using lentiviral vectors to ablate CXCR4 and/or CXCR7 expression, hiPSC-derived cardiomyocytes (hiPSC-CMs) were tested for phenotypic and functional properties due to gene knockdown. Gene expression confirmed cardiomyocyte phenotype of differentiated hiPSCs, although reduction of CXCR4 and CXCR7 expression resulted in delayed cardiac phenotype. Only knockdown of CXCR4 reduced the spontaneous beating of hiPSC-CMs. Knockdown of CXCR4 and CXCR7 differentially altered calcium transients and β-adrenergic response in hiPSC-CMs. In engineered cardiac tissues, depletion of CXCR4 or CXCR7 had opposing effects on developed force. The transendothelial migration response to SDF-1 was suppressed by knockdown of either CXCR4 or CXCR7. In contrast, in a trans-well chemotaxis assay, only depletion of CXCR4 reduced hiPSC migration in response to SDF-1 indicating that both CXCR4 and CXCR7 have distinct roles in the SDF-1/CXCR4/CXCR7 axis as network coordinators of cardiogenic induction and mobilization of hiPSCs. We contend that gaining further insight into the molecular nuances of this phenomenon will provide new insights for optimization of the cardiac repair potential of cell-based therapies.

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