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Inhibition of nuclear Nox4 activity: effect on proliferative capacity in human stem cells

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Human amniotic fluid stem cells (AFSC) with multilineage differentiation capacity are novel sources for cell therapy. However, stem cell samples obtained form patients differ in cell proliferation activity. Futhermore in vitro expansion leads to senescence affecting differentiation and proliferative capacities. Reactive oxygen species (ROS) have been involved in the regulation of stem cell pluripotency, proliferation and differentiation. Redox-regulated signal transduction is coordinated by spatially controlled production of ROS within subcellular compartments. Transcription factors, and even kinases and phosphatases, have been described to be redox regulated in the nucleus. NAD(P)H oxidase family, and in particular Nox4, has been known to produce ROS in the nucleus, however the mechanisms and the meaning of this function remain largely unknown.

In the present study we show that Nox4 localization in AFSC nuclei corresponds to speackle domains, as well as OCT4 (octamer-binding transcription factor 4) and SOX2 (SRY-box containing protein 2), two pluripotency regulating proteins. Stem cells isolated from different amniotic fluids exhibit a proliferation rate inversely coupled with Nox4 presence into the nuclei. Furthermore, Nox4 nuclear expression (nNox4) increases during culture passages up to cell cycle arrest and the serum starvation causes the same effect.

With a decrease of Nox4 activity, obtained by protein downregulation or by inhibition with plumbagin, a decline of nuclear ROS production and of DNA damage occurs. Moreover plumbagin exposure reduces the binding between nNox4 nucleoskeleton components, as lamin A/C and matrin. The same effect was observed also for the binding with phospho-ERK, although nuclear ERK and P-ERK are unchanged.

Taken together, we purpose that nNox4 regulation may have important pathophysiologic effects in stem cell proliferation through modulation of nuclear signaling and DNA damage.