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Potential new role for ROS in the epigenetic regulation of gene expression

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The generation of Reactive Oxygen Species (ROS) as by-products of the highly efficient aerobic metabolism constitute an inescapable biochemical side effect that can be extremely harmful for cell viability, due to the irreversible oxidation of lipids, proteins and nucleic acids. Nevertheless, eukaryotic cells can also actively generate ROS as essential components of molecular mechanisms regulating key cellular processes, including proliferation and differentiation, through the oxidation of redox-sensitive proteins such as kinases and phosphatases. ROS production in ESCs is low as anaerobic glycolysis rather than oxidative phosphorylation (OxPhos) is favoured. A switch from glycolysis to OxPhos is observed during ESC differentiation and accumulating evidence suggests that ROS is an important signalling molecule for ESC differentiation. Here we propose that eukaryotic cells could use ROS to directly regulate DNA methylation and gene expression patterns through the oxidation of methylated cytosines at target gene promoters.

To test this hypothesis, we have used a Protoporphyrin IX-dependent photodynamic treatment (PT) tool to activate a transient production of non-lethal ROS levels in the feeder-independent E14 mouse embryonic stem cell line. Using this tool, we report that the endogenous production of non-lethal ROS levels promotes a cytosine demethylation of tested promoters suggesting that these oxygen derivatives may be involved in the regulation of gene expression patterns through the dynamic modulation of DNA methylation patterns.

Recent Publications

1. Thomson JP, Meehan RR. The application of genome-wide 5-hydroxymethylcytosine studies in cancer research. Epigenomics 2017, 9:77-91
2. Cole JJ et al. Diverse interventions that extend mouse lifespan suppress shared age-associated epigenetic changes at critical gene regulatory regions. Genome Biol 2017, 18:58.
3. Thomson JP et al. Loss of Tet1-Associated 5-Hydroxymethylcytosine Is Concomitant with Aberrant Promoter Hypermethylation in Liver Cancer. Cancer Res 2016, 76:3097-3108.
4. Nestor CE et al. 5-hydroxymethylcytosine remodeling precedes lineage specification during differentiation of human CD4+ T-cells. Cell Reports 2016, 16:559-570.
5. Carrasco E et al. Switching on a transient endogenous ROS production in mammalian cells and tissues. Methods. 109:180, 2016.
6. Fonda-Pascual P et al. In situ production of ROS in the skin by PDT as a powerful tool in clinical dermatology. Methods. 109:190, 2016.
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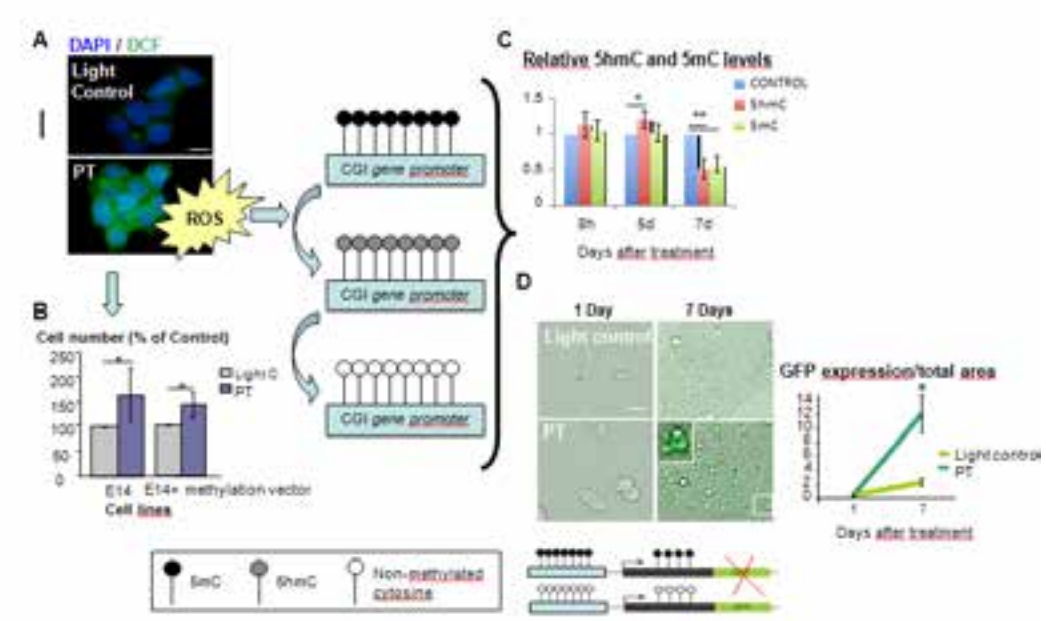

*Figure 1. Potential new role for ROS in the epigenetic regulation of gene expression (A) One single dose of PT generates non lethal ROS levels (DCF detection) that have physiological effects such as the stimulation of cell proliferation (B), but also could have other roles as the regulation of DNA methylation and gene expression, through the oxidation of the 5mC in CGIs. (C) DNA Dot Blot analysis quantification shows that 5 days after PT, there is an increase in 5hmC levels, followed by a decrease in 5hmC and 5mC levels 7 days after, compared to light control cells. (D) To test if the global reduction of 5mC levels is correlated to a change in transcription levels, a stable transfection with a methylation reporter gene (that expresses GFP when unmethylated) was performed. From 5 to 7 days after PT, a significant and gradual increase in GFP expression was detected, as shown in the images and in the graph. All images are representative of at least three independent experiments. Scale bar: 10 and 40 µm, A and D, respectively. The mean ± SD values of at least three independent experiments are represented in each graph. **: Significant, P ≤ 0.01. *: Significant, P ≤ 0,1.*

Biography

María Inmaculada Calvo Sánchez holds a postdoc position in the Experimental Dermatology and Skin Biology Group of the IRYCIS, Ramón y Cajal University Hospital. The research of this group is focused on cutaneus regenerative medicine and epigenetic changes induced by reactive oxygen species. Also she collaborates with the Francisco de Vitoria University as an associate professor in the degree of Biotechnology and in the Master's Degree in Advanced Therapies and Biotechnology Innovation, and as a coordinator of the practical part of the Masters mentioned above.

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