NADPH oxidase-1 plays a key role in UVB-induced carcinogenesis

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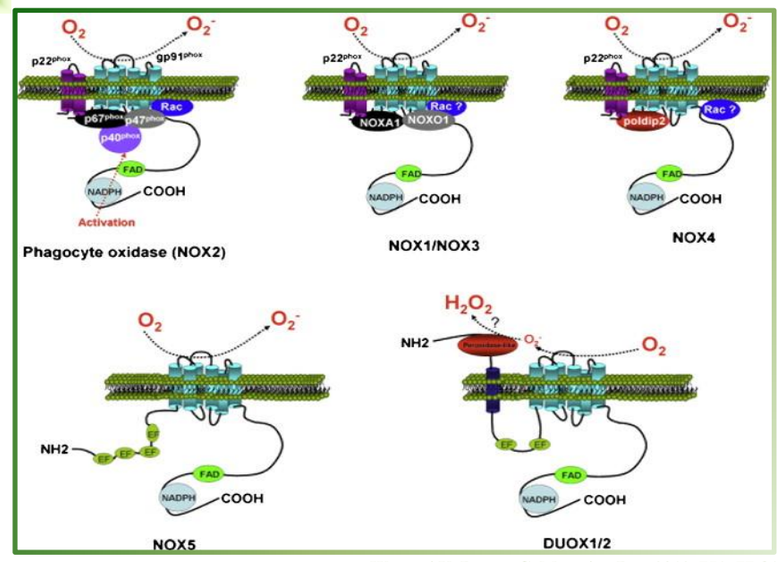
Introduction

Reactive oxygen species (ROS) are important molecules that have dual effects. On the one hand, increase in ROS concentrations results in redox imbalance and subsequent oxidative stress, leading to cytotoxicity through protein, lipid, and DNA oxidation both *in vitro* and *in vivo*. On the other hand, ROS can also act as second messenger molecules mediating the response of cells to various stressors. Therefore, evaluation and exploitation of the differential ROS levels and its downstream signaling between normal and cancer cells is emerging as a valuable therapeutic target. Compared with normal cells, cancer cells including squamous cell carcinomas (SCC) cells exhibit increased ROS levels. However, the sources of ROS generation and their contributions to SCC initiation and progression have not been fully defined.
Others and we have already highlighted that NADPH oxidase (NOX) could be the source of UVB-induced ROS generation (Rahman et al, 201; Rezvani et al. 2006; Rezvani et al. 2007; Ryu et al. 2010). However, it has not yet been fully defined which members of the NOX family is responsible of UVB-induced ROS generation in keratinocytes and what role this NOX might play in UVB-induced carcinogenesis. Of note, the NOX family includes 7 members: NOX1 to NOX5, Duox1 and Duox2. The NOX family enzymes involve in several physiological functions including host defense, post-tranlational processing of proteins, cellular signaling, regulation of gene expression, and cell differentiation. However, they differ in their tissue distribution and their activation mechanisms. For instance, NOX1-3 are inactivate in resting cells. To be active, they need to be assembled with the membrane-bound $p22^{phox}$ and their respective cytoplasmic subunits (**A**)(Altenhofer et al. 2015; Bedard and Krause 2007).

Objectives:
1. Which members of the NOX family is activated following UVB?
2. What role might NOX play in keratinocyte responses to UVB irradiation and UVB-induced carcinogenesis?

A



Weyemi U, Dupuy C, Mutation Res, 2012, 751: 77-81

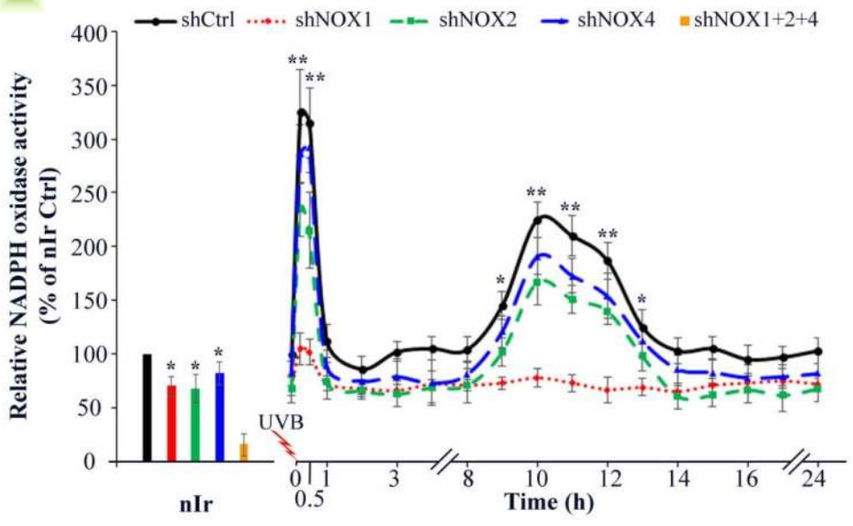
NADPH oxidase generates a large amount of superoxide anion radical ($O2^{\bullet}$) upon activation via the one electron-reduction of oxygen by NADPH. The classical phagocytic type of NADPH oxidase consists of six hetero-subunits, gp91phox (also termed Nox2), p22phox, p40phox, p47phox, and p67phox, as well as the small Rho GTPase, Rac. Six human homologous of Nox2 have been identified: Nox1, Nox3, Nox4, Nox5, Duox1, and Duox2.

NOX1, NOX2 and NOX4 are expressed in keratinocytes.

Results

1. UVB irradiation induces a biphasic activation of NOX-1

B



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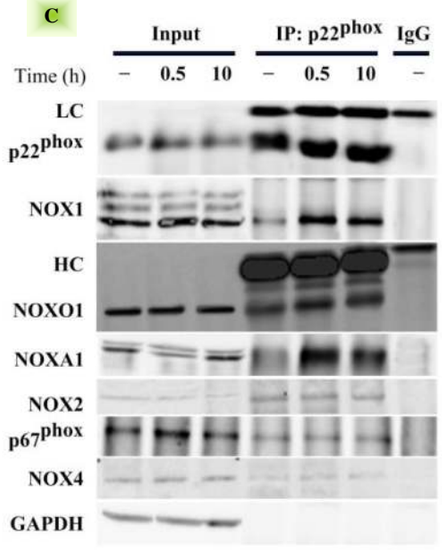
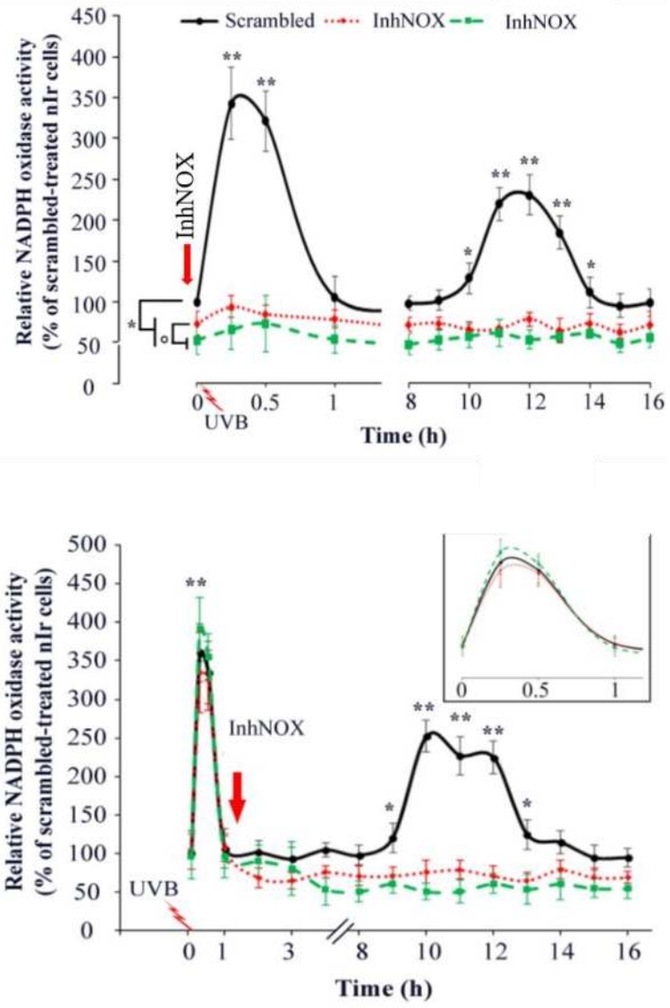


2. Pre-treatment of keratinocytes with InhNOX increases removal of UVB-induced DNA damage and decreases apoptosis

D



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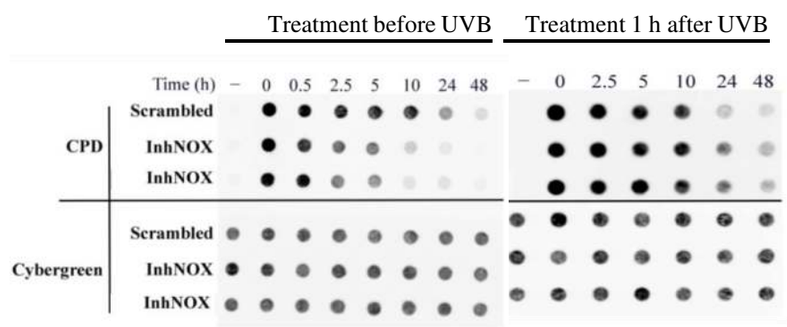

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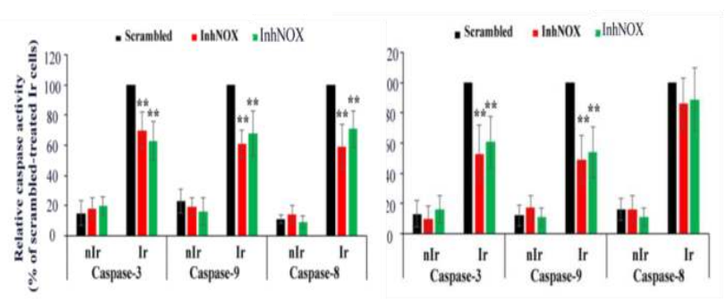
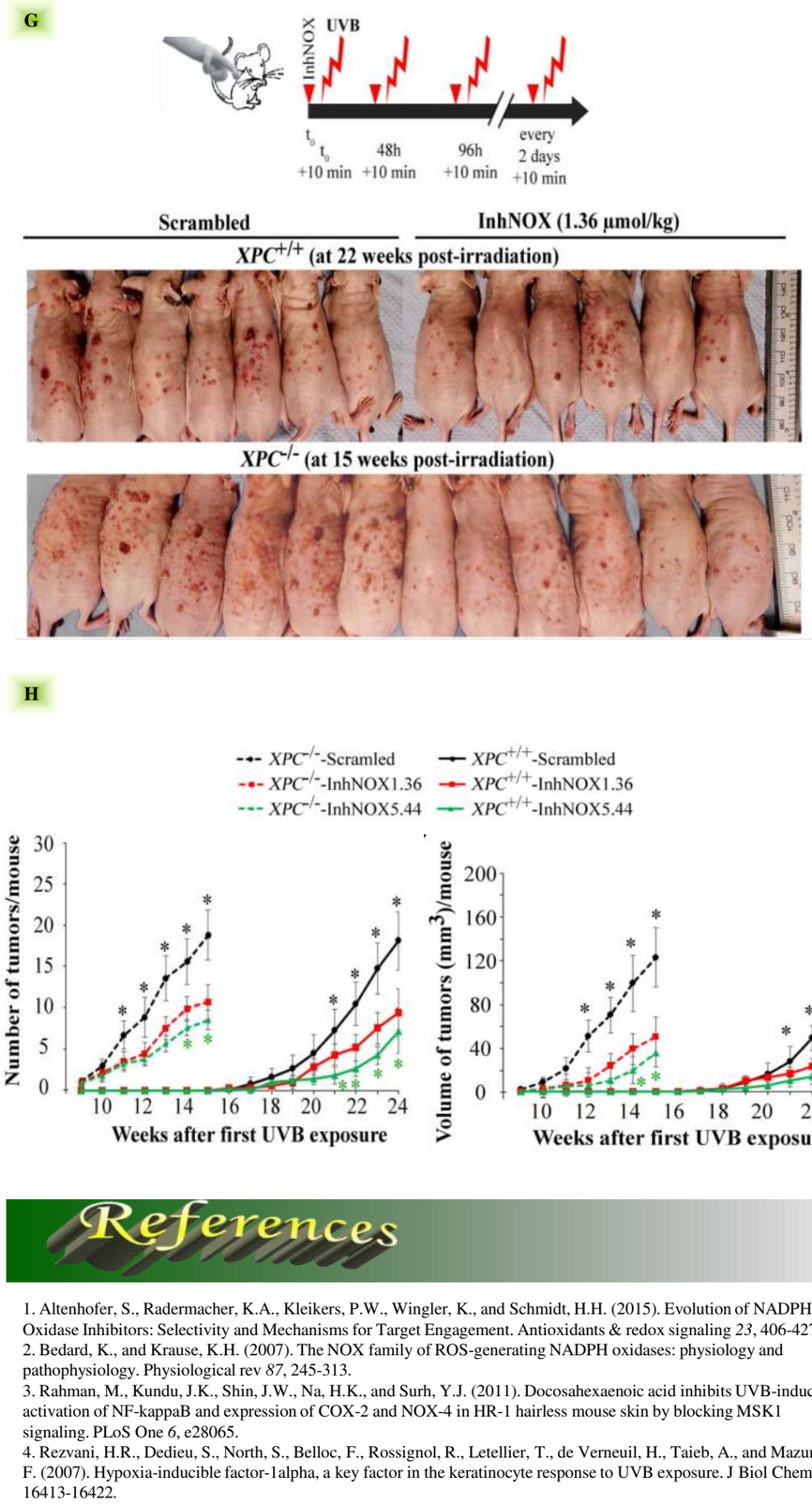


3. InhNOX treatment reduces photocarcinogenesis in XPC-proficient and -deficient mice

G



H

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