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## Impact of hypoxia on the pro inflammatory phenotype of human prostate cancer cell lines with different degree of differentiation

Ravenna Linda

Institute of Molecular Biology and Pathology, Italy

In tumors, hypoxia induces a transcription program that promotes an aggressive phenotype. Recent studies have suggested that hypoxia is also a feature in prostate cancer and is associated with a poor prognosis. The hypoxia-inducible factors (HIF)  $\alpha$  are the key transcription factors controlling the cellular response to hypoxia. Furthermore, prostate tumor progression is correlated with inflammation which is mainly regulated by NF- $\kappa$ B. A cross-talk between the NF- $\kappa$ B and the HIF pathways has been documented. The present study explored the hypoxic remodeling of the pro-inflammatory gene expression related to malignancy and the role of NF- $\kappa$ B in this process in well differentiated androgen dependent LNCaP and in less differentiated, androgen independent, highly metastatic DU145 and PC3 tumour prostate cells. Hypoxic treatments were carried in a sealed modular incubator chamber. NF- $\kappa$ B inhibition was obtained by parthenolide. Gene expression was evaluated by real time PCR and western blot. HIF1 was the main player in the response to hypoxia in all the examined cell lines while HIF2 did not appear modulated. A nuclear HIF3 $\alpha$  protein was detectable only in DU145 and a late hypoxic induction was observed. Hypoxia activated the NF- $\kappa$ B pathway in DU145 and PC3 but not in LNCaP cells. DU145 and PC3 cells evidenced a higher normoxic expression and a more complete hypoxic induction of a representative subset of pro-inflammatory molecules with respect to LNCaP cells. NF- $\kappa$ B inhibitor parthenolide counteracted the hypoxia induced phenotype in DU145 and in PC3 but not in LNCaP cells. These results show that in androgen-dependent more differentiated tumor, the contribution of epithelial cell to the pro-inflammatory gene expression in both normoxia and hypoxia is low as compared to that of advanced cancer. Besides, NF- $\kappa$ B plays a crucial role in shifting the hypoxic DU145 and PC3 but not LNCaP cells towards a pro-inflammatory, more malignant phenotype. The author intend to silence HIF-1 $\alpha$  to discriminate the specific role of HIF-1  $\alpha$  and NF- $\kappa$ B in this process. The knowledge of different involvement of these two pathways in different tumour phenotype could have useful fallout on clinical research and therapy.

### Biography

Ravenna Linda is a Researcher at the National Council of Research, Institute of Molecular Biology and Pathology, Roma, Italy. She graduated in Biological Sciences (1975), Researcher at Farmitalia Carlo Erba (1976-1981), Specialized in Microbiology (1987). She completed her PhD in Experimental Medicine (1995) and has published several papers in reputed journals. Her research interests are: a) Mutagenicity tests for new pharmaceutical molecules and mycotoxins. b) Effects of androgens and anti-androgens on proliferation, EGF, EGFR and AR expression in prostate cell lines. c) Estrogen regulation of EGFR transcription: molecular mechanisms and effects of selective estrogen receptors modulators (SERMs) d) Pro-inflammatory gene expression in prostate tumors. Role of hypoxic microenvironment on the activation of Hypoxia Inducible Factors, NF- $\kappa$ B and in the modulation of the pro inflammatory phenotype in prostate tumor cell lines.

[linda.ravenna@uniroma1.it](mailto:linda.ravenna@uniroma1.it)