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## LYSYL OXIDASE, HYPOXIA INDUCIBLE FACTOR –1 ALPHA AND INDUCIBLE NITRIC OXIDE SYNTHASE AS POSSIBLE BIOLOGICAL MARKERS IN BLADDER CANCER

**Shaymaa M. Mohammed**

PH.D. Clinical Chemistry / Department of pharmacy / Al-Mustaqbal University, Babylon- Iraq

**B**ladder Cancer (BC) is the commonest malignancy of the urinary tract ; it is a heterogeneous disease, with 70% of patients presenting with superficial tumors, that tend to recur and are generally not life threatening, About 30% of BC cases presenting as muscle-invasive disease associated with a high risk of death from distant metastasis. Several molecules and pathways have been identified to be linked to the pathogenesis of bladder cancer; while major efforts was directed to characterize molecular alterations to improve disease prognostication, only a few biomarkers of potential clinical relevance have been identified. The hallmark of cancer comprise of six biological capabilities acquired during the multistep development of human tumors, forming an organizing principle for rationalizing the complexities and diversity of neoplastic disease. They include sustaining proliferative signaling, evading growth suppressor, enabling replicative immortality and resisting cell death. In the past decades, majority efforts of cancer research have focused on the functional consequences of oncogene and tumor suppressor gene mutations. However tumors are complex tissues composed of multiple distinct cell types and the extracellular matrix (ECM), these participate in heterotypic interactions with one another in the genesis of tumors by influenceing the tumor microenvironment . Features of the tumor microenvironment that are significantly different from normal tissue are the reduction in oxygen pressure (PO<sub>2</sub>) which is indicated by hypoxia and pH reduction (acidosis) . Two important means by which cancer cells adapt to their microenvironment, by reprogramming cellular glucose / energy metabolism to use pathways that generate ATP in the absence of oxygen, and by stimulating angiogenesis to increase oxygen delivery. The microenvironment of solid tumors, is exposed to low oxygen tension (hypoxia), a key regulator of the cellular oxygen - signaling pathway is the Hypoxia Inducible Factor-1 $\alpha$  (HIF-1 $\alpha$ ) , a transcription factor that facilitate adaptation to oxygen deprivation by regulating the expression of genes that control cell metabolism, angiogenesis, cell proliferation and apoptosis. On the other hand, lysyl oxidase enzyme (LOX), an important modulator of extracellular matrix, is one critical HIF-1 $\alpha$  targets having an important role in the tumor development and progression. Furthermore, hypoxia associated with the maintained inflammatory state, resulted in activation of inducible nitric oxide synthase (iNOS), resulting in nitric oxide (NO) release, a further interesting affecter in the tumor microenvironment. Hypoxia-inducible factors (HIFs) are important angiogenic molecules, as they control a cell's response to a hypoxic stress. Over expression of hypoxia inducible factor -1 alpha (HIF-1 $\alpha$ ) has been demonstrated in many types of cancer with poor prognosis; its prognostic value is even more significant when combined with p53.