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Biomedical significance and ameliorative potentials of inducible nitric oxide synthase (iNOS) inhibitors in the development, progression and Metastasis of Prostate Cancer: A review

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Nitric oxide (NO) is synthesized in a variety of tissues and organs in a reaction where the amino acid L-arginine is converted into L-citruline. The enzyme catalyzing this reaction is designated as nitric oxide synthase (NOS). Inducible nitric oxide synthase (iNOS) is one of the three different isoforms of nitric oxide synthase. Aside the desirable effects of enhanced neurotransmission and vasodilation produced by the constitutive isoforms (nNOS and eNOS), the inducible isoform (iNOS) is associated with cytotoxicity of macrophages and tumor-induced immunosuppression. Expression of (iNOS) in various human tumors has been classically demonstrated in which case it promotes the progression of such tumors. The selective expression of iNOS has been reported in human prostrate carcinoma and thus nitric oxide consequently produced may have many roles in the development, progression and metastasis of prostate cancer. Prostatic intraepithelial neoplasia (PIN) significantly characterizes the development and progression of prostatic adenocarcinoma and has been associated with high levels of iNOS. Interestingly debates over PIN distribution and expression of (iNOS) is gaining momentum and points to the potentials of inducible nitric oxide synthase inhibitors in the amelioration of this development and progression. The immunohistochemical examination of the activity of iNOS in prostatic carcinoma has been significantly demonstrated in both basal epithelial cells and secretory cells of the glandular epithelium. Though nitric oxide produced by iNOS can have cytotoxic and cytostatic effects on tumor cells, and may act as tumor growth suppressors, its identified role in promoting angiogenesis in tumor suggests that it may stimulate tumor growth rather than inhibit it. There are conflicting information on the specific role of NO in cancer growth. While some hold the opinion of NO acting as a tumor suppressor others suggest that it actually promotes cancer growth hence a dual role. Recent findings suggest that NO may be relevant for tumor progression through at least two mechanisms: the stimulation of angiogenesis and increased mutagenesis through the direct action of free radicals on the DNA. In addition, NO released from tumor cells is suggested to participate in the tumor-induced immunosuppression via the anti-proliferative effect of NO on tumor-infiltrating lymphocytes. Many evidences abound regarding the strong association between iNOS expression and rapid prostate cancer cell proliferation rate, depicting a good predictor of poor survival in univariate analysis, but was inferior to established prognostic factors in multivariate analysis. From the various experimental observations, all three isoforms of NOS can be involved in promoting or inhibiting the etiology of cancer including prostate cancer in humans. NOS activity has been detected in tumor cells of various histogenetic origins and has been associated with tumor grade, proliferation rate, and expression of important signaling components associated with cancer development such as the estrogen receptor. Increased NO generation in a cell may select mutant P53 cells and contribute to tumor angiogenesis by upregulating vascular endothelial growth factor (VEGF). Due to the importance of NO in various pathological processes including prostatic carcinoma, NOSes are regarded as an important pharmacological target and a great deal of effort has been made to design specific NOS inhibitors. However, the high degree of similarity among NOS isoforms poses an obstacle when attempting to find a specific inhibitor of a particular isoform. From the upcoming experimental observations on the expression of NOS IN prostate carcinoma, it becomes very apt to suggest that inhibiting the production of NO synthesis by iNOS inhibitors would provide great opportunities and potentials for the management and amelioration of prostatic carcinoma. Therefore, an understanding of the molecular dynamics of NO in prostatic carcinoma would be very valuable in the development of drugs that potentially can be helpful in adult male prostate cancer patients.

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