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*STYK*1/*NOK*—A Potential Radiotherapeutic Target and Biomarker for Gastric Cancer and Cervical Cancer

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ABSTRACT

This article introduced the *STYK*1/*NOK*, including its origin, chemical composition and biological function, and the expression of *STYK*1/*NOK* in various cancer cell lines was reviewed. Furthermore, our recent study showed that *STYK*1/*NOK* protein was also over expressed in gastric cancer and cervical cancer specimens, and *STYK*1/*NOK* expression increased after tumor cells were irradiated with γ ray. These results indicated that *STYK*1/*NOK* might be involved in the occurrence and progress of gastric cancer and cervical cancer, and contribute to the radioresistance of tumor cells. Thus, *STYK*1/*NOK* might be a potential therapeutic target and diagnostic marker for gastric cancer and cervical cancer.

Keywords: Gastric Cancer; Cervical Cancer; *STYK*1/*NOK*; Therapeutic Target

1. Introduction

It is well known that receptor tyrosine kinases (RTKs) is perhaps the most important and extensively studied pathway. Ligand binding results in receptor autophosphorylation and the subsequent activation of downstream signalling cascades that include mitogen-activated protein kinase (MAPK), extracellular-signal-regulated kinase (ERK), phosphatidylinositol 3-kinase (PI3K), phospholipase Cγ, protein kinase C and small GTPases such as Ras, Rho and RAC1 (Ras-related C3 botulinum toxin substrate 1). Abnormal expression of RTKs was believed to contribute to the tumorigenesis and progression.

*STYK*1 (*Serine*/*Threonine*/*Tyrosine Kinase* 1), also named *NOK* (*The novel oncogene with kinase-domain*) encoding a potential kinase, has been cloned in 2004 by Liu, L. *et al*. [1]. *STYK*1/*NOK* is approximately 30% similar to the mouse fibroblast growth factor (FGF) and platelet-derived growth factor (PDGF) receptor super-family, and is predicted to have a transmembrane domain and protein kinase domain, belonging to a receptor protein tyrosine kinase family. Many studies suggested that *STYK*1/*NOK* were involved in oncogenesis and metastasis [1,2], previous studies have shown that *STYK*1/*NOK* mRNA was up-regulated in various cancer, including breast cancer and lung cancer [3,4].

2. *STYK*1/*NOK* Genes Studies Development in Gastric Cancer and Cervical Cancer

Gastric cancer was the fourth most common cancer and the second leading cause of cancer death worldwide [5-8]. It has been well proved that RTKs are involved in the occurrence and progress of gastric cancer. Furthermore, RTKs-targeted agents, such as Cetuximab [9], Trastuzumab [10-12], have been applied for treatment of the gastric cancer.

Besides melanoma cells (B16), lung cancer cells (A549), breast cancer cells (MCF-7, MDA-MD-123), the expression of *STYK1/NOK* was detected in gastric cancer cells (BGC823) and cervial cancer cells (Hela), Moreover, our recently study showed that *STYK*1/*NOK* protein was also over expressed in gastric cancer and cervical cancer specimens. However, the normal tissues rounding cancer expressed relative lower *STYK*1/*NOK* protein. Interestingly, real-time PCR results showed that the expression of *STYK*1/*NOK* mRNA in tumor cells increased after 2 - 10 Gy of γ-ray radiation, which indicated that *STYK*1/*NOK* might participate in the regulation of cancer radio-

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resistance. These results indicated that *STYK*1/*NOK* might be a potential therapeutic target and diagnostic marker for gastric cancer and cervical cancer, and treatment targeting *STYK*1/*NOK* might show a synergism with radiotherapy for gastric cancer and cervical cancer. However, there is still a long way to go for the application of *STYK*1/*NOK*, because all the studies on *STYK*1/ *NOK* was restricted to laboratory.

3. Discussion

The human *STYK*1/*NOK* is widely expressed in human tissues with the highest abundance in the prostate, brain and heart [13]. Besides normal tissues, a variety of tumor cells also expressed the *STYK*1/*NOK* mRNAs [3], such as CRPC（castration-resistant prostate cancer）cells [14]. *STYK*1/*NOK* could promote cell transformation, tumorigenesis, and metastasis [1]. In cells, *STYK*1/*NOK* was localised in endosomes and colocalised with epidermal growth factor receptor (EGFR) [15]. *STYK*1/*NOK* could mediate STAT3 signaling pathway, RAS/MAPK signaling pathway and PI3K/AKT signaling pathway [1,16,17], and form complexes with both Akt and GSK-3β [2]. Mutation of a tyrosine residue at Y417 site in the catalytic *STYK*1/*NOK* domain decreased the tumorigenic potential of tumor cells *in vivo*, suggesting an oncogenic role for *STYK*1/*NOK* [18]. Mutations both Y356F and Y356F significantly impaired Akt phosphorylation and accelerated cell death by activating caspase-3-mediated pathways, but did not affect the kinase activity of *STYK*1/*NOK* [19]. *STYK*1/*NOK* is up-regulated in estrogen receptor-alpha negative estrogen receptor-beta positive breast cancer cells following estrogen treatment [3]. *STYK*1/*NOK* is over expressed in ovarian cancer [20], lung cancer [4], breast cancer [19] and acute leukemia [21]. *STYK*1/*NOK* mRNA expression did not correlate with c-erbB2 expression, indicating the independence of *STYK*1/*NOK* as a diagnostic marker in breast cancer of tiny tumors in which the malignancy cannot be confirmed by other means [19].

The role study of *STYK*1/*NOK* in gastric cancer and cervical cancer is not reported up to now. Our group is trying to study on this field, and obtained some results. Our preliminary results, together with previous studies, indicate that *STYK*1/*NOK* could be a possible therapeutic target and biomarker for gastric cancer and cervical cancer.

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