FOXM1 induced by E6 oncoprotein promotes tumor invasion and chemoresistance in HPV-infected lung cancer

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Induction of FOXM1 expression by E6 oncoprotein via the MZF1/NKX2-1 axis is responsible for soft-agar growth, invasiveness, and stemness in HPV-positive oral and lung cancer cells. Among patients, the presence of HPV16/18 DNA was positively correlated with NKX2-1 and FOXM1 expression in oral and lung tumors. When oral or lung cancer patients were individually divided into four subgroups by two parameters (HPV and FOXM1), HPV-positive oral or lung cancer patients with high-FOXM1 tumors exhibited the worst overall survival and relapse free survival among the four subgroups of both cancers. Xenograft lung tumor nodules in nude mice injected with HPV-positive oral and or lung cancer stable clones were markedly diminished by FOXM1 inhibitor (thiostrepton). Therefore, we suggest that FOXM1 may potentially represent a therapeutic target in HPV-positive oral or and lung cancer patients with HPV16/18-positive tumors.

Keywords: HPV; FOXM1; oral cancer; lung cancer

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Persistent high-risk human papillomavirus (particularly HPV16, HPV18) infection is considered to be the strongest risk factor for genital-related cervical, vulvar, and anal carcinomas [1, 2]; and non-genital-associated head and neck squamous cell carcinomas and lung cancer [3, 4]. The involvement of HPV infection in Taiwanese oral and lung tumorigenesis has been extensively studied [5-8] although the negative correlation between HPV infection and lung cancer has been reported elsewhere [9-11]. Therefore, the geographic variation has been considered to explain the difference in the association between HPV infection and lung cancer.

The E6 and E7 proteins in high-risk HPV act as primary transforming viral proteins to inactivate the p53 and Rb pathways which results in cell proliferation and resistance to apoptosis [12]. This leads to the accumulation of DNA damage and mutations that give rise to cell transformation and carcinoma development [12]. For example, the positive correlation of HPV16/18 infection with increased ROS levels, DNA damage, and the risk of EGFR mutation occurrence has been shown in Taiwanese NSCLC patients [13]. Further insights into the mechanistic action of the E6 and E7 oncoproteins on tumor progression should be investigated.

Foxhead box M1 (FOXM1) overexpression has been shown to be correlated with tumor progression and poor prognosis in various human carcinomas, including oral cancer and lung cancer [14-17]. FOXM1 controls oxidative stress to prevent cell senescence and apoptosis [18]. FOXM1 also regulates cell cycle-related gene expression, such as cyclin B1, cyclin D1 and cdc25 expression, so as to promote cervical tumor progression [19]. Wang and colleagues showed that proliferation of lung tumor cells was diminished in Mx-Cre FOXM1-/- mouse mutants and that these mice had a significant reduction in tumor formation efficacy [20]. In contrast, tumors from FOXM1 transgenic mice treated with
3-methylcholanthrene/butylated hydroxytoluene displayed a significant increase in tumor formation efficacy compared with wild-type mouse tumors [20]. Conversely, the efficacy of tumor formation was remarkably reduced when FOXM1 was deleted from mouse respiratory epithelial cells [21].

FOXM1 is upregulated by E2F1, which is released by Rb phosphorylation via p53 inactivation [22, 23]. FOXM1 expression in HPV-associated tumor progression remains unclear. It is expected that FOXM1 expression suppressed by wild-type p53 may be de-repressed by E6-degraded p53. Our mechanistic studies indicate that E6 plays a crucial role in the upregulation of FOXM1 transcription in HPV-associated tumor, which is in contrast to previous reports that showed FOXM1 up-regulation by E2F1 released by Rb phosphorylation via p53 inactivation [22, 23, 25]. FOXM1 interacts with HPV16 E7 to promote the transformation of primary rat embryo fibroblasts [24]. Here, we provide evidence that E7 does not affect FOXM1 expression in HPV-positive cervical, oral and lung cancer cells [25].

We recently reported that FOXM1 upregulated by HPV E6 oncoprotein promotes cell proliferation, anchorage independent growth, and invasiveness in oral and lung cancer cells [25]. Furthermore, FOXM1 transcription is predominantly regulated by the E6-dependent NKX2-1 through the MZF1 expression [25]. HPV-mediated FOXM1 expression is predominately through NK2 homeobox 1 (NKX2-1) induced by E6 oncoprotein [25]. The fact can be evidenced by that FOXM1-mediated invasiveness is diminished by NKX2-1 silencing. Therefore, we suggest that FOXM1 induced by E6 oncoprotein is responsible for HPV-associated lung and oral tumor progression [25].

FOXM1 promotes cell stemness, and glioma tumourigenesis via activating Wnt/β-catenin signaling pathway [26-28]. Consistently, the activation of the Wnt/β-catenin signaling pathway is expected to be
responsible for cell stemness mediated by E6-induced FOXM1 expression and therein the spheres formed assay show that self-renewal capability of E6-induced FOXM1 cells is increased [25]. The expression of Nanog, Oct4 and c-Myc elevated by E6-mediated FOXM1 were responsible for cell stemness in E6-positive oral and lung cancer cells [25].

FOXM1 expression has been shown to be associated with chemoresistense in human gastric cancer [29], breast cancer [30, 31], ovarian cancer [32], and lung cancer [33]. Sixty-one of 110 lung cancer patients were available to examine the possibility that FOXM1 expression could be associated with the response to cisplatin-based chemotherapy. As shown in Table 1, patients with high-FOXM1 tumors were more commonly to have unfavorable response to cisplatin-based chemotherapy than those with low-FOXM1 tumors (HR, 3.939, 95 % CI, 1.329-11.673, P = 0.011). This result was consistent with previous report [33] to reveal that FOXM1 expression was associated with chemotherapeutic response in lung cancer with or without HPV infections. Chemoresistance induced by high-FOXM1 tumors may be through induction of EMT and stemness by E6-mediated FOXM1 expression. We thus strongly suggest that FOXM1 inhibitor thiostrepton might not only result in tumor regression but also confer chemosensitivity in HPV-infected oral and lung cancer.

In summary, upregulation of FOXM1 by E6 Oncoprotein via the MZF1/NKX2-1 axis is required for initiation of cancer stem-like cells and in turn, differentiates cell invasiveness, and chemoresistant in HPV-infected oral and lung cancer. Therefore, we suggest that FOXM1 might be potential therapeutic target for HPV16/18-positive oral and lung cancer. The possible pathway of E6-induced FOXM1 in HPV-associated tumorigenesis is addressed in Figure 1. Notably, a similar mechanism of E6-mediated FOXM1 observed in HPV-positive oral and lung cancer, reveals the fact that E6-induced FOXM1 may contribute to HPV-infected lung tumorigenesis in Taiwan.

Conflicting interests

The authors have declared that no competing interests exist.

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