

Expression of Minichromosome Maintenance Protein 7 and Smad 4 in Squamous Cell Carcinoma of the Esophagus

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Received : December 15, 2009
Accepted : February 16, 2010

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Background : Minichromosome maintenance protein 7 (MCM 7) performs a direct role in the initiation of DNA replication, which suggests that it may prove useful as a marker of cell proliferation. *Smad 4* is a tumor suppressor gene that mediates the transforming growth factor β pathway. The principal objective of this study was to characterize the expression of MCM 7 and Smad 4 and to analyze their relationship to clinicopathological parameters in patients with esophageal squamous cell carcinoma. **Methods :** Expression levels of MCM 7 and Smad 4 were evaluated via immunohistochemistry on formalin-fixed and paraffin-embedded tissues from 67 cases of esophageal squamous cell carcinoma. **Results :** High levels of MCM 7 expression were detected in 53 cases (74.6%), and were associated with higher T stages ($p = 0.030$). Kaplan-Meier survival curves demonstrated that patients with higher levels of MCM 7 expression had poorer prognoses, although this association was not significant ($p = 0.086$). Loss of Smad 4 expression was noted in 18 cases (23.4%), and was not associated with clinicopathological characteristics, including MCM 7 expression, or prognosis. **Conclusions :** MCM 7 expression is associated with the invasiveness of esophageal squamous cell carcinoma. Altered expression of Smad 4 does not appear to have pathobiological significance in esophageal carcinoma.

Key Words : MCM protein 7, human; Smad 4 protein, human; Carcinoma, squamous cell; Esophageal neoplasms

Esophageal cancer is the 9th most common cancer in Korean males.¹ Squamous cell carcinoma is the most common histological type worldwide, including in Korea. Risk factors thus far identified are cigarettes, alcohol, lack of vitamin A, C, and E, lack of folic acid, a history of achalasia, corrosive esophagostenosis, hyperkeratosis, Plummer-Vinson syndrome, and head and neck tumors.²⁻⁴ The esophagus lacks a serosal layer, although the lymphatic channels are well-developed, and early-stage esophageal cancer spreads readily into the adjacent organs, thus resulting in an overall poor prognosis. This poor prognosis issue persists, despite recent improvements in surgical methods and therapeutic agents.⁵ Although several previous studies have focused on the identification of prognostic molecular markers in this cancer, no significant prognostic markers have yet been identified.

The minichromosome maintenance (MCM) complex is a DNA-binding heterohexamer complex formed by minichromosome maintenance proteins 2-7 (MCM 2-7). The MCM complex functions as a "licensing factor," which allows the initiation of DNA replication. During cell division, it allows only

one DNA replication per cycle. The MCM complex combines with the origin recognition complex, Cdc 6, and Cdt 1 to form the prereplicative complex (pre-RC).⁶⁻¹⁰ Once the pre-RC is built up, the initiation of DNA replication is permitted. During DNA synthesis, the MCM complex dissociates from the replication origin, thereby preventing replication from occurring until the cell achieves the G1 phase of the next cycle.⁶⁻¹⁰ MCM proteins are thought to be useful markers for proliferation, as it has been demonstrated in replicating but not quiescent cells.¹¹⁻¹³ Additionally, MCM proteins are utilized as markers for the diagnosis of invasive cancer and carcinoma *in situ*. Recent studies have demonstrated an increase in MCM proteins in malignant tumors such as adenocarcinoma of the lung, colon, and prostate, papillary thyroid carcinoma and endometrial carcinoma.¹¹⁻¹⁶ A few studies have also evaluated the expression of MCM 2, 4, and 5 in esophageal squamous cell carcinoma, but, to the best of our knowledge, no research into MCM 7 expression in esophageal carcinoma has been reported thus far in the English-language literature.¹⁷⁻¹⁹

The transforming growth factor β (TGF- β)/Smad pathway is