MCM2 - a promising marker for premalignant lesions of the lung: a cohort study

ABSTRACT

We conclude that MCM2 is detectable in 2-3 times more proliferating premalignant lung cells than is Ki-67. The promise of MCM2 as a sensitive marker for premalignant lung cells is enhanced by the fact that it is present in cells at the surface of metaplastic lung lesions, which are more likely to be exfoliated into sputum. Future studies will determine if use of anti-MCM2 makes possible sufficiently early detection to significantly enhance lung cancer survival rates.

INTRODUCTION

Introduction The 5-year survival rate for patients with lung cancer is approximately 15%, and it has changed only marginally in the last 30 years. Tumor stage is the most significant prognostic parameter for 5-year survival, but even patients with non-small cell lung cancer (non-SCLC) in pathologic stage IA disease (a tumor of less than 3 cm diameter located in one lobe of the lung and more than 2 cm from the carina without visceral pleural involvement, atelectasis, or pneumonitis, and absence of metastatic spread to regional lymph nodes) have a 33% chance of recurrence within 5 years after complete surgical resection (lobectomy with mediastinal lymph node dissection). In this group of patients, the tumor most frequently recurs at distant sites, including the bone, liver, adrenal glands, and brain, and the size of the primary tumor does not appear to impact on survival. This suggests that even small and seemingly resectable lung cancers metastasize early. Data from randomized screening trials for lung cancer corroborate this observation. In these studies, more cancers were detected in resectable stages, and 5-year survival rates were higher in the screened population compared to the control population, but mortality rates (total death rate independent of time) from lung cancer were equal in both groups. For this reason, it is important to develop methods that will permit facile detection of bronchial mucosal abnormalities that are precursors for lung cancer before systemic shedding of tumor cells occurs. Such precursor lesions can be detected by sputum cytology and by bronchoscopy in large airways accessible by endoscopy. They include metaplasia, dysplasia, and carcinoma in situ (CIS), which are thought to represent progressive histologic correlates of carcinogenesis for squamous cell carcinoma. Current data suggest that 23% of current and former smokers have metaplastic lesions, and 2% have dysplastic lesions. However, not all such lesions progress to lung cancer. For instance, smoking cessation, which can be viewed as a form of active intervention, appears to result in a decrease of metaplasia rates from 27% in active smokers to 7% in former smokers. It is estimated that approximately 50% of CIS will progress to invasive cancer over a 6-month time period. However, of 9 patients followed by regular bronchoscopy at 6-month time intervals, 4 developed lung cancer at sites that had previously been biopsied and interpreted as normal bronchial epithelium. These results raise several important questions: A) Are there determinants in premalignant lesions that predict outcome, i.e., progression versus regression? B) Are there determinants in morphologically normal bronchial mucosa that predict outcome? C) Can lung cancer arise directly from normal bronchial mucosa or are histopathologic intermediates required? To address these questions, one promising approach would be the development of specific immunohistochemical markers capable of improving the sensitivity and reliability of methods currently employed to

detect precursor lesions in histologic and cytologic specimens. Because proliferation is a requirement for lung cancer development, markers specific for cell proliferation are expected to prove useful. Two proliferation markers, proliferating cell nuclear antigen (PCNA) and Ki-67, have been extensively studied in this context. PCNA is a homotrimeric protein that binds tightly to DNA and to proteins involved in DNA replication and repair. It is essential for DNA replication and is found in all proliferating cells. However, because PCNA is also essential for several types of DNA repair, it may be present in non-proliferating cells. Ki-67 is an epitope of a nuclear protein recognized by the MIB-1 monoclonal antibody. The protein is frequently expressed throughout the cell cycle of proliferating cells, and it has not been detected in non-proliferating cells. During interphase, Ki-67 is located primarily in nucleolar and peri-nucleolar regions, and it appears to be associated with condensed chromatin. The function of the Ki-67 protein is still unknown, however, it appears to be required for cells to progress through the cell cycle. Immunohistochemical studies with PCNA and Ki-67 indicate that, in at least some cases, increased lung tumor staining for these markers correlates with decreased survival. These proliferation markers can also be detected in premalignant lesions of the lung. In this report, we describe the results of our comparison of one of these classic proliferation markers, Ki-67, with a new proliferation marker, MCM2. MCM2 is one of six members of the minichromosome maintenance (MCM) protein family. These serve as components of "licensing factor," which is essential for initiation of DNA replication and for limiting replication to one round per cell cycle. The MCM proteins are also associated with replication forks and are likely to stimulate the unwinding of the parental DNA strands at these forks. We previously demonstrated that, in normal tissues, MCM2 is detectable only in proliferating cells. Not surprisingly, it is also present in a high proportion of cancer cells. Our results showed a higher proportion of positively stained cells in premalignant breast lesions than with either PCNA or Ki-67. Others have reported similar results for MCM family proteins compared with Ki-67 and PCNA for detection of a variety of premalignant cell types, but a comparison of MCM proteins with Ki-67 or PCNA as markers for premalignant lung lesions has not previously been reported.

CONCLUSION

We have confirmed that polyclonal anti-MCM2 antibodies provide consistent, reliable staining in routinely fixed tissues without a requirement for antigen retrieval. Results obtained are easy to interpret, since there is a striking difference between normal bronchoepithelium and premalignant lesions. Thus MCM2 is an easy-to-use marker, which has great potential for assessment of progression and regression of morphologically abnormal lesions in future primary lung cancer prevention studies and for the early detection of lung cancer in screening studies.