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Commentary Article
Bronchioloalveolar neoplasia

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Abstract: Bronchioloalveolar carcinoma (BAC) arising in the peripheral lung is the prototype of human lung adenocarcinoma and is considered to develop, at least in part, from its precursor atypical adenomatous hyperplasia (AAH). Molecular genetics investigations have revealed the significant roles of mutations in *KRAS* and *epidermal growth factor receptor* (*EGFR*) genes in the pathogenesis of AAH and BAC. Recently, selective molecular targeting therapies, such as those using EGFR tyrosine kinase inhibitors, have been introduced with remarkable success. In spite of the accumulation of research results into BAC/AAH, there remain three important issues to be addressed; 1) the etiology of BAC and AAH, 2) the genetic and/or epigenetic alteration(s) responsible for the progression of AAH to BAC, 3) the genetic backgrounds speculated as the cause of multiple AAH/BAC. These three issues are briefly reviewed and discussed, along with the murine pulmonary carcinogenesis model which is potentially useful for solving these issues.

Keywords: Bronchioloalveolar carcinoma, atypical adenomatous hyperplasia, *KRAS* gene, *epidermal growth factor receptor* gene, molecular targeting therapy, murine model

Lung cancer is one of the most prevalent human cancers and the leading cause of cancer-related deaths [1-3]. Human lung cancers are extremely heterogeneous, among which adenocarcinoma is the most common histological type [3]. Bronchioloalveolar carcinoma (BAC) arising in the peripheral lung is the prototype of human lung adenocarcinoma. It is generally accepted that BAC, at least in part, develops from its precursor atypical adenomatous hyperplasia (AAH) in the fashion of the adenoma-carcinoma sequence [4-6], like the colonic adenoma-carcinoma-developing process [7]. In contrast to colonic carcinogenesis, however, where *KRAS* gene mutations play a role in malignant conversion [7], the genetic and/or epigenetic alteration(s) responsible for the progression of AAH to BAC remains unknown. It is plausible that some or the majorities of AAHs remain stable or even regress and that some BACs develop *de novo*. In the latter case, it is probable that genetic alterations occur simultaneously or cumulatively over a very short period of time. The peripheral lung progenitor cell (Clara, type 2, or other specified cell) is considered the origin of AAH and BAC [3-6]. Molecular genetics investigations have revealed the significant roles of mutations in *KRAS* and *epidermal growth factor receptor* (*EGFR*) genes in the pathogenesis of AAH and BAC [8,9]. Accordingly, selective molecular targeting therapies, such as those using EGFR tyrosine kinase inhibitors, have been introduced with remarkable success [10]. Multiple BAC and AAH lesions are not infrequently observed in patients who undergo resection of the lung for lung cancer, particularly BAC-type adenocarcinoma [11-13]. The etiology of BAC and AAH has not been clarified, as most patients with BAC and/or AAH are either non-smokers or have no history of exposure to known carcinogens [9,10]. Tobacco smoking, however, is considered responsible for the progression of non-invasive/early BAC to invasive/advanced BAC (mixed-type adenocarcinoma with BAC pattern) through *TP53* gene alterations and *p16/INK4A* gene silencing [3-6,9]. In regard to multiplicity, certain genetic backgrounds are speculated as the cause of multiple AAH/BAC [14-16], but few have been elucidated. The murine pulmonary carcinogenesis model is highly useful for understanding the pathogenesis and genetic background of human AAH/BAC, because mouse

lung tumors are almost analogous to human AAH/BAC in terms of the phenotype, developing process, and genetic alterations [3-6,14,15]. For instance, susceptible genes have been discovered by cross-mating susceptible and resistance strains along with gene-chip microarray analysis [15-19]. Furthermore, recent investigations have focused on a series of mouse strains engineered to carry mutations in genes known to be involved in human cancer [3-6,10,20-23]. The results of investigations into AAH and BAC, particularly those regarding its pathology, pathogenesis, and molecular genetics in humans, as well as those obtained from murine models, have opened a new strategy of molecular targeting therapies, as described above. The fruits of research into AAH/BAC are one of the most representative models in the area of medical sciences in the sense of the successful integration of clinical investigations, pathological and molecular genetics analyses of human materials, and animal models. Thus, this example potentially provides a novel paradigm in research and for developing prevention/therapy strategies not only of lung cancer but also of other kinds of malignant neoplasia. Finally, it is underscored that future studies should focus principally upon the etiology of AAH/BAC, the genetic and/or epigenetic alteration(s) responsible for the progression of AAH to BAC, and the genetic background of multiple AAH/BAC lesions.

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