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ORIGINAL ARTICLE

# AKR1B10 in usual interstitial pneumonia: Expression in squamous metaplasia in association with smoking and lung cancer

Chih-Ping Li[a], Akiteru Goto[a], Akira Watanabe[b], Kengo Murata[a], Satoshi Ota[a], Toshiro Niki[c], Hiroyuki Aburatani[b], Masashi Fukayama[a,*]

[a]*Department of Human Pathology, Graduate School of Medicine, The University of Tokyo, Hongo 7-3-1, Bunkyo-ku, Tokyo 113-0033, Japan*
[b]*Genome Science Division, Laboratory for Systems Biology and Medicine, Research Center for Advanced Science and Technology, The University of Tokyo, Tokyo, Japan*
[c]*Department of Pathology, School of Medicine, Jichi Medical School, Tochigi, Japan*

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## Abstract

The incidence of lung cancer (LC) is markedly increased among patients with usual interstitial pneumonia (UIP), and tobacco smoking is its superimposed risk factor. AKR1B10 (aldo-keto reductase 1B10) is frequently overexpressed in pulmonary squamous cell carcinoma and adenocarcinoma in smokers. To investigate the role of AKR1B10 in the pulmonary carcinogenesis in UIP with correlation to tobacco smoking, we examined 13 UIP cases with LC, 13 UIP cases without LC, and 30 cases of non-UIP LC using AKR1B10 immunohistochemistry. AKR1B10 immunoreactivity was confined to squamous metaplasia in honeycomb lesions of UIP and neoplastic cells of LC. Squamous metaplastic foci showed AKR1B10 immunoreactivity more frequently in UIP with LC (24/36 foci, 67%) than in UIP without LC (16/44 foci, 37%) ($P<0.01$). AKR1B10 expression in UIP was also more frequent in squamous metaplastic foci in smokers (38/67 foci, 57%) than in non-smokers (2/13 foci, 15%) ($P<0.01$). AKR1B10 expression was frequently observed in both UIP-associated LC (10/13 foci, 77%) and non-UIP LC (18/30 foci, 60%). Ki-67 labeling index was significantly higher in AKR1B10-positive squamous metaplasia of UIP than in AKR1B10-negative squamous metaplasia of UIP. Our results demonstrate that AKR1B10 is involved in the development of LC in UIP in association with smoking. AKR1B10 might be useful as a new marker for identification of high LC risk patients in UIP.


***Keywords:*** Usual interstitial pneumonia/idiopathic pulmonary fibrosis (UIP/IPF); AKR1B10; Lung cancer; Squamous metaplasia; Tobacco smoking

## Introduction

Usual interstitial pneumonia (UIP) is the most common interstitial pneumonia [1]. UIP has also been described as cryptogenic fibrosing alveolitis, and a large proportion of the UIP lung corresponds to the clinical entity known as idiopathic pulmonary fibrosis (IPF). The incidence of lung cancer (LC) is markedly increased in UIP patients both in Western countries [10] and in Japan [9,14]. Moreover, epidemiological studies demonstrate a close association between tobacco smoking and high cancer risk in UIP [14]. However, the exact

*Corresponding author. Tel.: +81 3 5841 3344; fax: +81 3 3815 8379.
*E-mail address:* mfukayama-tky@umin.ac.jp (M. Fukayama).

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mechanism of LC development in UIP with correlation to tobacco smoking is not fully known yet. Recent research revealed that *AKR1B10* (aldo-keto reductase 1B10) gene was one of the significantly upregulated genes in non-small cell LC (NSCLC) cell lines detected by oligonucleotide array, and its overexpression was frequent in NSCLC, especially in squamous cell carcinoma and also in heavy smokers' adenocarcinoma [7,25]. AKR1B10 belongs to the aldo-keto reductase (AKR) superfamily, a superfamily of monomeric NAD(P)H-dependent oxidoreductases that catalyze the reduction of carbonyl compounds [11], and AKR1B10 reduces aromatic and aliphatic aldehyde substrates [2].

In this study, we evaluated the possible roles of AKR1B10 in LC development in UIP with correlation to tobacco smoking by an immunohistochemical assessment of AKR1B10 expression with special reference to squamous metaplasia of honeycomb lesions in UIP. The proportion of squamous metaplasia was significantly higher in LC-positive UIP than in LC-negative UIP [9]. Moreover, it has been reported that molecular abnormality of fragile histidine triad (FHIT) was revealed in squamous metaplasia of UIP [22]. We also performed a study comparing the immunohistochemistry of AKR1B10 with that of p53 or Ki-67.

## Materials and methods

### Case selection

The cases were selected using two sources: a review of 5338 consecutive autopsies performed at the Department of Pathology, the University of Tokyo, from 1978 to 2004, and the surgical files of 195 resected lung cancers studied at the Department of Diagnostic

**Table 1.** Clinical features and results of AKR1B10 expression in UIP without/with lung cancer

| Clinicopathologic features of cases of UIP without/with lung cancer | | | | | | | Number of squamous metaplasia foci, examined foci/ identified foci/ number of slides | AKR1B10 immunoreactivity | |
|---|---|---|---|---|---|---|---|---|---|
| Case number | Material Source | Age[a] | Gender | Smoking history | Duration of IPF (months) | Lung cancer (histology) | | Squamous metaplasia −/+/++ | Cancer |
| 1 | A | 65 | M | Yes | 28 | No | 3/36/14 | 2/1/0 | Na |
| 2 | A | 64 | M | Yes | 30 | No | 3/4/10 | 3/0/0 | Na |
| 3 | A | 74 | M | Yes | 4 | No | 5/22/13 | 3/1/1 | Na |
| 4 | A | 94 | F | No | 44 | No | 2/2/11 | 2/0/0 | Na |
| 5 | A | 71 | F | No | 23 | No | 4/7/6 | 2/0/2 | Na |
| 6 | A | 64 | M | Yes | 85 | No | 5/5/7 | 3/2/0 | Na |
| 7 | A | 67 | M | Yes | 1.5 | No | 5/12/10 | 2/1/2 | Na |
| 8 | A | 68 | M | Yes | 1 | No | 4/39/6 | 0/0/4 | Na |
| 9 | A | 78 | M | Yes | 11 | No | 3/6/4 | 2/0/1 | Na |
| 10 | A | 65 | F | Yes | 9 | No | 3/11/14 | 2/1/0 | Na |
| 11 | A | 76 | F | No | 9 | No | 2/16/10 | 2/0/0 | Na |
| 12 | A | 74 | M | Yes | 76 | No | 3/5/7 | 3/0/0 | Na |
| 13 | A | 64 | F | No | 45 | No | 2/4/12 | 2/0/0 | Na |
| 14 | A | 66 | M | Yes | 8 | Yes (SQ) | 3/7/14 | 0/2/1 | + |
| 15 | A | 81 | M | Yes | 16 | Yes (SQ) | 1/2/7 | 1/0/0 | − |
| 16 | A | 67 | M | Yes | 60 | Yes (SQ) | 1/2/3 | 0/0/1 | + |
| 17 | A | 73 | M | Yes | 99 | Yes (SQ) | 1/2/7 | 0/0/1 | + |
| 18 | S | 75 | M | Yes | 3 | Yes (SQ) | 6/12/13 | 2/2/2 | ++ |
| 19 | S | 73 | M | Yes | 50 | Yes (SQ) | 3/13/14 | 0/1/2 | ++ |
| 20 | A | 69 | M | Yes | 14 | Yes (SQ) | 1/1/4 | 0/0/1 | − |
| 21 | A | 60 | M | Yes | 5 | Yes (SQ) | 2/2/5 | 2/0/0 | ++ |
| 22 | S | 63 | M | No | 0[b] | Yes (SQ) | 3/3/9 | 3/0/0 | − |
| 23 | S | 61 | F | Yes | 0[b] | Yes (SQ) | 3/6/13 | 0/1/2 | ++ |
| 24 | S | 63 | M | Yes | 61 | Yes (SQ) | 1/2/9 | 1/0/0 | ++ |
| 25 | A | 63 | M | Yes | 13 | Yes (AD) | 7/9/4 | 1/0/6 | ++ |
| 26 | A | 73 | F | Yes | 29 | Yes (AD) | 4/7/4 | 2/1/1 | ++ |

−, <10% or no cells stained; +, 10–50% cells stained; ++, >50% cells stained. A, autopsy case; S, surgically resected specimen; M, male; F, female; SQ, squamous cell carcinoma; AD, adenocarcinoma; na, not associated with lung cancer.

[a]Age of death in cases from autopsy files or age of surgery in cases from surgical files.

[b]UIP was newly diagnosed at admission for surgery of lung cancer.