Lung: non-small cell carcinoma with inv(2)(p21p23)

Hiroyuki Mano

Division of Functional Genomics, Jichi Medical University, 3311-1 Yakushiji, Shimotsukesashi, Tochigi 329-0498, Japan (HM)

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Clinics and pathology

Disease

A subset of non-small cell lung cancer harbors the EML4-ALK fusion gene. Incidence of such tumors is 4-5% in non-small cell lung cancer among the Asian ethnic group, but may be lower among the others.

Genetics

Note

Vast majority of EML4-ALK positive lung cancer is negative for active EGFR and active KRAS.

Cytogenetics

Note

inv(2)(p21p23)

Genes involved and proteins

Note

Inv(2)(p21p23) involves EML4 and ALK, generating the EML4-ALK and ALK-EML4 fusion genes.

EML4

Location

2p21

Protein

981 amino acids; 109 kDa; microtubule associated protein.

ALK

Location

2p23

Protein

1620 amino acids; 176 kDa; membrane-associated tyrosine kinase receptor.

Result of the chromosomal anomaly

Hybrid Gene

Note

In lung cancer cells, 5'-part of EML4 is fused to intron 19 of ALK, generating EML4-ALK. While intron 19 of ALK is involved in the rearrangement in most of the cases, breakpoints within EML4 may diverge, giving rise to various isoforms of EML4-ALK. Detailed information of known variants is shown below.

EML4-ALK(E13;A20): Intron 13 of EML4 is ligated to intron 19 of ALK, generating an EML4-ALK mRNA where exon 13 of the former is fused to exon 20 of the latter (also referred to as variant 1).

EML4-ALK(E20;A20): Intron 20 of EML4 is ligated to intron 19 of ALK, generating an EML4-ALK mRNA where exon 20 of the former is fused to exon 20 of the latter (also referred to as variant 2).

EML4-ALK(E6;A20): Intron 6 of EML4 is ligated to intron 19 of ALK, generating an EML4-ALK mRNA where exon 6a of the former is fused to exon 20 of the latter.

Alternative splicing of the messages gives rise to the E6a; A20 (variant 3a) and E6b; A20 (variant 3b) mRNAs, which contains exon 6a and 6a+6b of EML4, respectively.

EML4-ALK(E14;ins11;del49A20): Another rearrangement generates an EML4-ALK mRNA where exon 14 of EML4 is ligated to a fragment of 11 bp with
unknown origin, and in turn connected to a nucleotide at position 50 of exon 20 of ALK (also referred to as variant 4 by Takeuchi et al.).

**EML4-ALK(E15del19;del20A20):** Another rearrangement generates an EML4-ALK mRNA where a part of exon 15 of EML4 is fused to a nucleotide at position 21 of exon 20 of ALK (also referred to as variant 4 by Koivunen et al.).

**EML4-ALK(E2;A20) and EML4-ALK(E2;add117A20):** Intron 2 of EML4 is ligated to intron 19 of ALK, generating an EML4-ALK mRNA where exon 2 of the former is fused to exon 20 of the latter (also referred to as variant 5a). From the same gene rearrangement, alternative splicing of messages further generates an mRNA where exon 2 of EML4 is connected to a position within intron 19 of ALK located 117 bp-upstream of exon 20 (also referred to as variant 5b).

**Fusion Protein**

**Note**

All EML4-ALK fusion mRNAs encode proteins where a part of EML4 is fused to the cytoplasmic kinase domain of ALK. The amino-terminal coiled-coil domain within EML4 is necessary and sufficient for the transforming activity of EML4-ALK, probably through oligomerizing the fusion proteins.

**References**


This article should be referenced as such: