Polimorfisme hypoxia inducible factor 1a (HIF) 1 dan hubungannya dengan instabilitas genetik pada kanker paru = Hypoxia inducible factor 1a polymorphisms are associated with genetic aberrations in lung cancer

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Abstrak

Latar Belakang: Faktor transkripsi Hypoxia inducible factor-1 (HIF-1 merupakanpengatur utama hipoksia, termasuk menyebabkan penekanan sistem perbaikan deoxyribose nucleic acid (DNA), sehingga menghasilkan instabilitas genetik pada sel kanker. Varian genetik HIF-1 C1772T (P582S) dan G1790A (A588T) dipercaya mempunyai aktivitas transkripsi yang lebih tinggi.Peranan polimorfisme HIF-1 ini sudah diteliti pada beberapa jenis kanker seperti kanker ginjal, payudara, ovarium, tetapi belum ada penelitian pada kanker paru.
Metode: Polimorfisme HIF-1 diperiksa dengan menggunakan direct sequencing dengan total sampel 83 pasien kanker paru (42 adenokarsinoma, 30 skuamous sel karsinoma, empat adenoskuamous sel karsinoma dan tujuh kanker paru karsinoma sel kecil (KPKSK) dan 110 subjek sehat sebagai kontrol. Hubungan polimorfisme HIF-1 dengan kelainan genetik/epigentik loss of heterozygot (LOH) TP53, LOH 1p34, LOH retinoblastoma-1 (RB1), inaktivasi p16 dan kelainan epidermal growth factor receptor (EGFR) kemudian diperiksa.
Hasil: Frekuensi polimorfisme HIF-1 pada kanker paru dan kontrol telah sesuai dengan keseimbangan Hardy-Weinberg. Pada penelitian ini tidak ditemukan perbedaan frekuensi genotipe C1772T atau G1790A antara kanker paru dengan kontrol sehat. Tetapi, frekuensi varian HIF1A C1772T ditemukan tinggi bermakna di pasien kanker paru dengan LOH TP53 (p=0,015). Pada pasien adenokarsinoma, individu dengan varian alel memiliki frekuensi tinggi LOH TP53 (p=0,047), LOH 1p34 (p=0,009) atau keduanya (LOH TP53 dan LOH 1p34) (p=0,008). Aktivitas transkripsi juga diperiksa secara in vitro dan ditemukan HIF1A varian pada sel kanker paru A549 mempunyai aktivitas yang meningkat secara bermakna dibanding wild type HI1F1A baik di kondisi normoksia atau hipoksia, terutama P582A di sel dengan mutan p53 (p< 0,0005 dan p< 0,005).
Kesimpulan: Penelitian ini mengindikasikan polimorfisme gen HIF-1 mempunyai peranan penting dalam karsinogenesis paru terutama pada adenokarsinoma, diduga melalui peningkatan instabilitas genetik.
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Background and objective: The transcription factor, hypoxia-inducible factor-1 (HIF-1), is a master regulator of hypoxia, including repression of DNA repair systems, resulting in genomic instability in cancer cells. The roles of the polymorphic HIF-1a variants, C1772T (P582S) and G1790A (A588T), which are known to enhance transcriptional activity, were evaluated in lung cancers.
Methods: HIF-1a polymorphisms were assessed by direct sequencing in a total of 83 lung cancer patients (42 adenocarcinomas, 30 squamous cell, four adenosquamous cell and seven small cell lung carcinomas) and in 110 healthy control subjects. The relationship between these polymorphisms and the frequently observed genetic and/or epigenetic aberrations, TP53 loss of heterozygosity (LOH), 1p34 LOH, retinoblastoma-1 (RB1) LOH, p16 inactivation and epidermal growth factor receptor aberrations, was then assessed.

Results: There were no significant differences in genotype frequencies for either C1772T or G1790A between lung cancer patients and healthy controls. However, the frequency of the HIF1A C1772T variant allele was significantly higher in lung cancer patients with TP53 LOH ($P = 0.015$). Among adenocarcinoma patients, individuals with variant alleles of either polymorphism showed significantly higher frequencies of TP53 LOH ($P = 0.047$), 1p34 LOH ($P = 0.009$), or either of these ($P = 0.008$) in the tumours. The in vitro transcriptional activity of these HIF1A variants in A549 lung cancer cells was significantly greater than that of the wild type under either normoxic or hypoxic conditions, especially for P582S in cells containing mutant p53 ($P < 0.0005$ and $P < 0.005$, respectively).
Conclusions: These findings indicate that functional polymorphisms in the HIF-1a gene may have an important impact on lung carcinogenesis, especially in adenocarcinomas, possibly by increasing genomic instability.