ERCC1 (excision repair complementing defective repair in Chinese hamster)
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Identity
Hugo: ERCC1
Location: 19q13.32.

DNA/RNA
Description
14 305 bp and 10 exons.
Transcription
1,101 bps.

Protein
Description
297 amino acids.
Expression
ERCC1 is expressed at higher levels in tumor tissue compared to normal tissue and the expression shows more inter-individual variation among cancer patients than among healthy individuals. ERCC1 expression and ERCC1 protein levels in tumor tissue may predict response to chemotherapy. Thus, non-small cell lung cancer patients with undetectable ERCC1 protein levels in tumor tissue had a longer survival after cisplatin-based adjuvant chemotherapy than patients with detectable ERCC1 protein levels. However, high ERCC1 protein levels were associated with increased survival among patients who were not treated with chemotherapy.

Function
ERCC1 was originally identified as a gene that complemented a certain DNA repair defective Chinese Hamster Ovary cells (CHO) UV20. ERCC1 forms a heterodimer with XPF (also called ERCC4) to form the endonuclease which makes the 5’ incision during nucleotide excision repair. ERCC1 mRNA levels in lymphocytes correlate positively with DNA repair capacity measured by host cell reactivation. ERCC1 mRNA levels correlate closely with XPD, OGG1 and RAI mRNA levels in lymphocytes.

In case-control studies of lung cancer patients, lung cancer patients were shown to have lower mRNA levels and lower DNA repair capacity than healthy controls. This was also found in a case-control study of head and neck cancer. However, in a prospective study of lung cancer, persons, who were later diagnosed with lung cancer did not have a lower ERCC1 mRNA level than those who did not get lung cancer, indicating that the low ERCC1 expression level observed in cancer patients may be a result of the disease rather than a cause.

ERCC1 expression seems to be inducible at least at the mRNA level. Thus, the expression of ERCC1 in human lymphocytes correlated with increased solar influx indicating that UV irradiation may induce ERCC1 expression. In mice, X-ray irradiation lead to increased ERCC1 expression in lung tissue, and ingestion of diesel exhaust particles increased ERCC1 expression in liver. This indicates that ERCC1 expression is inducible, and thus that ERCC1 expression levels may rather be a biomarker of the internal dose of DNA damage than a biomarker of DNA repair capacity or a mix of the two.

Mutations
Note: One of the most frequently studied polymorphisms in ERCC1 is ERCC1 Asn118Asn (rs11615). Homozygous carriers of the haplotype
ERCC1 Asn118Asn, ASE-1 G-21AG, PPP1R13L IVS1 A4364GA have been shown to be at increased risk of breast cancer and lung cancer. The ERCC1 Asn118Asn polymorphism was found not to correlate with mRNA levels. ERCC1 C8092A (rs3212986) was found to interact with smoking in relation to risk of lung cancer in a large case-control study. ERCC1 C8092A was found not to correlate with mRNA levels in peripheral blood cells.

Implicated in

Breast cancer

Prognosis

Thus, women who were homozygous carriers of the haplotype had a 9.5-fold higher risk of breast cancer before 55 years of age than women who were not homozygous carriers. Older women and heterozygous carriers were not at an increased risk of breast cancer.

Lung cancer

Disease

Homozygous carriers of the haplotype were found to be at 4.9-fold increased risk of lung cancer in the age interval 50-55 years. The association was stronger among women than among men, although the difference was not statistically significant. In subsequent study including more cases and a larger comparison group, a statistically significant difference between genders was found. Furthermore, it was found that the haplotype interacts with smoking intensity. Thus, among women, who were carriers of the haplotype, additional smoking at high smoking intensity (>20 cigarettes/day) was associated with increased lung cancer risk. This was not seen among women who were not homozygous carriers of the haplotype or among men.

The haplotype was not associated with risk of testis cancer or with risk of colorectal adenomas or colorectal cancer. Furthermore, the haplotype was not associated with risk of basal cell carcinoma among older persons (>60 years). These results indicate that the haplotype may be associated with risk of cancer primarily among young and middle aged persons and that it may be specific for women.

Leukemia and bladder cancer

Disease

The variant allele of ERCC1 Asn118Asn has also been combined with the polymorphisms XPD Asp312Asn and XPD Lys752Gln in haplotype analysis. Here, the haplotype GAT was associated with increased risk of leukemia and bladder cancer among non-smokers and the ACC haplotype was associated with lowered risk of bladder cancer.

Colorectal cancer, small cell lung cancer, and non small cell lung cancer

Disease

Carriers of the variant allele of ERCC1 Asn118Asn were found to have a worse prognosis of colorectal cancer, small cell lung cancer and non-small cell lung cancer, whereas no association with risk of colorectal cancer has been found.

References


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