

Értekezés címe: Genetic and epigenetic background of melanoma progression
Szerző: Ecsedi Szilvia, DE NK Megelőző Orvostani Intézet Biomarker analízis Tanszék

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Summary

The main purpose of the doctoral thesis was to provide a comprehensive genetic and epigenetic study to define somatic DNA alterations that contribute to the aggressive biological behavior of human primary melanomas.

1. Investigating genome-wide (transposable) DNA methylation:

- We demonstrated the strong influence of *LINE1* transposable demethylation in the metastatic formation of primary melanomas during the follow-up period.

2. Studying regional (localized) DNA methylation:

- The methylome, presenting in early stage samples and associated with the *BRAF*^{V600E} mutation, decreased in the more advanced stages of the disease.
- Local coordinated allele loss and DNA hypermethylation was shown at the region of 6q22-q23 that encodes the *MYB1* and *EYA4* genes.
- We revealed that the 19p13.2 genomic region harboring *DNMT1* gene (DNA methyltransferase-1 responsible for the maintenance of methylation patterns during DNA replication) often suffers from DNA copy number loss in melanomas thicker than 4 mm.
- The DNA methylation changes of the *KIT* gene was significantly associated with shortened relapse-free survival in melanoma patients.

3. Integrative genomic analysis:

- A set of genes with copy number loss were defined in ulcerated malignant melanomas, which were significantly enriched on chromosome 6q and 10q. Most of the genes were involved in cell-cell and cell-matrix adhesion or apoptosis.
- The first evidence for trans-acting copy number changes was given in melanomas.
- The expression and methylation patterns of additional genes exhibited an inverse correlation, suggesting that transcriptional silencing of these genes is driven by epigenetic events.

In conclusion, we demonstrated the strong influence of genome-wide as well as regional DNA methylation changes on melanoma progression. Methylation pattern was demonstrated to be a part of an integrated apparatus of somatic DNA alterations. We identified functionally relevant molecular hotspots characterised by copy number losses and promoter hypermethylation that might indicate a poor clinical outcome of melanoma.

Kulcsszavak: malignus melanoma, daganat progresszió, epigenetika

Keywords: malignant melanoma, tumor progression, epigenetics