# Genetic and gene expression alterations during melanoma progression

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Malignant melanoma is an aggressive, therapy-resistant malignancy of melanocytes. The incidence of the disease has been steadily increasing worldwide, resulting in an increasing public health problem. The interactions between genetic and environmental risk factors that promote melanomagenesis are currently subject of ongoing research. At present, there are no systemic agents available that significantly extend the lifespan of patients with advanced disease, and the key to improved survival in all affected individuals remains early diagnosis and treatment.

We applied high throughput Affymetrix microarray technology on a series of primary and metastatic melanomas with known clinical follow-up. Furthermore to define the genetic background of gene expression changes we used array CGH in combination with interphase FISH targeting EGFR oncogene and 9p21 tumorsuppressor locus.

Two characteristic molecular subclasses of primary melanoma were identified by unsupervised cluster analysis, segregating aggressive tumors from the less aggressive ones. Volcano plot analysis showed 1095 differently expressed genes in the ulcerated melanoma group. Majority of these genes (1021 genes) were down regulated in this set of tumors and upregulated in the less aggressive group. Using array CGH no copy number alterations were seen in most of the down regulated genes. Metastatic melanomas displayed similar gene expression signature to the ulcerated melanomas. Using functional annotations (DAVID, Ingenuity) we could identify molecular pathways and defined that five networks belong into the hair and skin development-, cancer-cellular growth- and proliferation and affect the p53, Wnt/β-catenin and Nf-κB signaling pathways.

Using interphase FISH analysis we demonstrated that elevated copy number of EGFR gene is associated with poor prognosis in primary melanomas. Significant correlation was found between EGFR alterations and histological subtypes, tumor thickness, ulceration and metastases formation. Gene copy alterations were associated with elevated mRNA expression in 77% of lesions when compared to tumors with disomic EGFR status. The correlation between the gene amplification status and the level of mRNA and protein expression was not linear. It was found by LOH that deletion of the 9p21 tumorsuppressor locus is frequent alterations in primary melanomas. In order to define this alteration at the cellular level we

performed interphase FISH analysis on large number primary melanomas and found that the loss of 9p21 is frequent alteration in primary melanomas which is present in early and late stages of the disease with similar frequency. We did not find strong correlation between the 9p21 status of melanomas and patients' clinical parameters.

**Key words**: melanoma, gene expression, microarray, aCGH, FISH, EGFR, 9p21