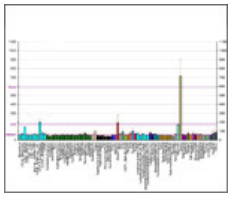
Novel Heritable Melanoma and Renal Cancer Factor Identified

By Anna Azvolinsky, PhD | October 19, 2011

Researchers have identified a novel rare, germline mutation linked to a predisposition for both melanoma and renal cell carcinoma (RCC) that results in a five-fold increased risk of developing melanoma, RCC, or both. The research is described in this week's *Nature* (DOI: 10/1038/nature10539). The findings provide insight into the molecular mechanisms underlying the etiology of the diseases.

According to Brigitte Bressac-de Paillerets of the Gustave Roussy Cancer Institute in Villejuif, France and colleagues, this is the first time that a genetic or environmental factor has been associated with melanoma and renal cancer, two diseases that generally have different risk factors. Melanoma is associated with high sun exposure, pigmentation and nevus phenotypes. RCC, on the other hand, is associated with smoking, obesity and hypertension. However, another recent study of melanoma and RCC support the hypothesis that there is a genetic predisposition underlying the association between the two cancers.



Gene expression pattern of the MITF gene; source: Wikimedia Commons, user BotMultichillT

Bressac-de Paillerets and colleagues proposed that a transcription factor called the microphthalmia-associated transcription factor (MITF), which has been suggested as a potential melanoma oncogene also confers a genetic predisposition to RCC. The rationale for the link is that MITF stimulates the transcription of the hypoxia inducible factor (HIF1A), which targets kidney cancer susceptibility genes.

Sequencing the MITF gene in 62 patients with melanoma and RCC, the team identified a germline heterozygous missense substitution, Mi-E318K, in five patients. Carriers of the mutation had a 14-fold higher risk than controls in developing both cancers. Additionally, the mutations were significantly higher among 603 melanoma-only patients compared to controls, conferring a greater than 4-fold risk of melanoma. The mutation was also associated with melanoma among three melanoma-prone families. The frequency of the mutation among RCC-only patients was also statistically significant.

The missense mutation results in a MITF protein with severely impaired SUMOylation, a post-translational modification added to proteins at specific amino acid sites. The addition of SUMO (small ubiquitin-like modifier) or SUMOylation, is implicated in a variety of different cellular processes through signal transduction.

The team determined that the Mi-E318K mutation activates the HIF1A promoter better than wild type. It was previously reported that SUMOylation of MITF represses its transcriptional activity; therefore, this newly identified missense mutation is an “up” mutation that increases the activity of the MITF transcription factor. A further genome-wide analysis confirmed that Mi-E318K has a higher occupancy of the HIF1A promoter as well as another promoter, HMOX1 that is involved in both kidney cancer and melanoma cell growth a well as an overall higher global transcriptional activity and impaired SUMOylation of MITF. The authors suggest that SUMOylation likely regulates the way MITF interacts with its target gene promoters.

This is the first identification of a predisposition to cancer mutation that is lined to impaired SUMOylation according to Brigitte Bressa-de Paillerets. “BRCA1 is sumoylated but no mutation in the sumoylation site has been described to date” she said.

A genomic expression profile of an RCC cell line expressing either wild-type or the Mi-E318K MITF protein showed that the mutant-expressing cell line had a 32-gene signature of up- and down-regulated genes associated with proliferation,

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cell growth, and inflammation. As these experiments were conducted in transformed cell lines, whether this higher occupancy results in higher expression in both tumor types still needs validation.

Bressac-de Paillerets and team also established that the Mi-E318K mutation is more potent than wild-type in "promoting invasive and tumorigenic behaviors in melanoma and RCC cells." While the mutant protein did not significantly stimulate melanoma or RCC cell growth, the researchers suggest that this is in parallel with melanoma cell populations that have a higher rate of invasion and division potential but a generally slow growth rate. "Mi-E318K might favor a phenotypic switch of melanoma cells towards a tumor-initiating cell phenotype" the researchers conclude.

"We are [now] planning to look for a differential expression profiling of melanocytes cultured from the skin of Mi-E318K and Mi-WT patients, both in normal conditions and after various stresses. We want to study what happens at early transformation steps and whether or not it is linked to oxidative stress" Bressac-de Paillerets stated. "Our hypothesis is that the germline mutation impairs the appropriate cellular answer to stresses. This is indeed oncogenic as an initiating event but probably not enough at more advanced cancer stages," she further explained. This is why Bressac-de Paillerets said she was not surprised that sequencing of RCC and melanoma tumors did not find the Mi-E318K mutation. The mutation is crucial in early tumorigenesis but is likely not necessary to sustain tumor growth in advanced cancer.

The study provides a link between SUMOylation, transcription, and melanoma and RCC tumor formation and highlights the usefulness of mutation screening in genetically enriched cancer patient populations as a way to identify rare yet important genetic variants associated with a higher cancer risk. Further studies including studies in isolated primary tumors will further validate the role of the MITF missense mutation in both melanoma and RCC.

Bressac-de Paillerets believes that with further validation, families predisposed to RCC and melanoma will be screened for the newly identified mutation. "For melanoma risk assessment, testing in molecular diagnostics labs should arrive quickly in low sun exposure countries. As the mutation co-segregates within small melanoma-prone families, it is found more frequently in patients who developed multiple primary melanomas. Photo-protective behaviors should be strongly recommended to Mi-E318K mutation carriers. In high sun exposure countries, the mutation does not co-segregate in families and generally speaking, oncogeneticists and dermatologists are reluctant for testing of known melanoma predisposing genes such as CDKN2A and CDK4 because of the phenocopies risk," Bressac-de Paillerets elaborated for CancerNetwork.

"For kidney cancer, we need more data to perform appropriate counselling. The mutation occurs only in clinically sporadic cases. I suspect an important co-factor, either genetic or environmental," she said.

"We need to do more work to study the outcome of cancers in carriers of the Mi-E318K mutation. As an overall conclusion, this gives us a new research perspective in prevention and perhaps chemoprevention and possibly therapeutics," Bressac-de Paillerets concluded.

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