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Identification of Corticotropin Releasing Factor and Corticotropin Releasing Factor Receptor 1 and 2 in macrophages in melanocytic naevi and melanoma and correlation with clinical data

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Melanoma is a highly immunogenic tumor with a strong immune cell infiltrate that shows good responses to treatment with immune checkpoint inhibitors. Tumor-associated macrophages are the most abundant immune cell population in melanoma. Tumor-associated macrophages are a heterogeneous cell population composed of different subpopulations that remain ill-defined and cover a range from pro-inflammatory, potentially tumoricidal subpopulations to anti-inflammatory, tumor-supporting subpopulations. In the human skin, a stress response system was found with a duplicate of the hypothalamic-pituitary gland-adrenal axis with peripheral expression of Corticotropin releasing factor (CRH), Corticotropin releasing factor receptors (CRHR1 and CRHR2), and other hormones like Pro-opiomelanocortin, Adrenocorticotropic hormone and α-Melanocyte-stimulating hormone.
In this work, immunohistochemical and immunofluorescent stainings of human malignant and benign melanocytic lesions for CRHR1, CRHR2, CRH, and the pan-macrophage marker CD68 were performed. In the immunohistochemical stainings, CRHR1+ and CRHR2+ cells were identified with morphological features of macrophages. In the immunofluorescent stainings, a colocalization of CRHR1, CRHR2, CRH and CD68 could be identified in melanoma, while in benign melanocytic naevi only a very limited number of double-positive cells could be found.
A comparative analysis of immunohistochemical staings for CRHR1, CRHR2, CRH, and CD68 expression was performed with tissue-microarrays containing benign melanocytic naevi, primary melanomas and metastatic melanoma lesions and correlated with clinical data. A higher expression of CRHR1 was found in primary melanomas and naevi, CRHR2-expression was higher in naevi and metastatic melanomas, and CRH was higher expressed in primary melanoma. Regarding clinical data, females' CRH expression in metastatic melanomas was significantly higher than males. In males a high expression of CRH correlated with lower survival. In human M-CSF-stimulated pBM, a higher crhr1 expression was identified compared to MDI-stimulated pBM, while no crhr2 expression was detected and the human monocytic cell line U937 did not express crhr1 or crhr2.
Concluding, results of this work indicate that there are sex differences in regard to CRH expression in melanoma, which might influence the overall survival in men, but not in women. Generally, CRH expression is higher in melanoma compared to benign melanocytic lesions, but the expression of its receptors varies between primary and metastatic melanoma. While CRHR1 expression is downregulated in metastatic melanoma, which could limit an immunological response directed against melanoma cells and increase the metastatic rate, CRHR2 is upregulated by metastatic melanoma cells might leading to decreased cell adhesion and enhanced cell motility. Further functional assays and clinical data assessments are needed.