

# Melanoma and Mastocytosis

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## Abstract

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There are numerous cases reports and studies confirming the enhanced incidence of melanoma among patients with mastocytosis, especially with systemic mastocytosis. These two diseases are arising from two different types of cells; melanoma arises from neural crest cells and mastocytosis from hematopoietic stem cells. But there are a lot of similarities between the two diseases. The most important and significant is the dependence of the growth factor receptor c-KIT and c-KIT ligand (stem cell factor) for their growth and development. Also, expression of the STAT3 (signal transducer and activator of transcription 3) and transcription factors MITF (microphthalmia-associated transcription factor) make the connection between melanoma and mastocytosis.

## Introduction

There are numerous cases reports and studies confirming the enhanced incidence of melanoma among patients with mastocytosis, especially with systemic mastocytosis. These two diseases are arising from two different types of cells; melanoma arises from neural crest cells and mastocytosis from hematopoietic stem cells. But there are a lot of similarities between the two diseases. The most important and significant is the dependence of the growth factor receptor c-KIT and c-KIT ligand (stem cell factor) for their growth and development. Also, expression of the STAT3 (signal transducer and activator of transcription 3) and transcription factors

MITF (microphthalmia-associated transcription factor) make the connection between melanoma and mastocytosis.

## Discussion

Mastocytosis is a group of rare disorders characterised by the proliferation and accumulation of mast cells in the skin and/or other organs, and occur in children and adults. Most of the patients, about 80%, are with cutaneous mastocytosis, and mostly the course is indolent (90%). Classification of cutaneous mastocytosis is into urticaria pigmentosa, the most

common cutaneous variant, solitary mastocytoma and diffuse cutaneous mastocytosis.

Melanoma is one of the most malignant cancers, with the incidence increasing all over the world, and it is one of the most frequent cancers in fair-skinned populations. There are biological explanations for an increased incidence of melanoma among patients with mastocytosis. Mast cells would interact with melanocytes through the release of cytokines. The high rate of mutations in melanoma makes it difficult to distinguish between driver mutations and bystander mutations. The most frequent driver mutations in melanoma are BRAF, NRAS, KIT, GNAQ, GNA11, NF1 and telomerase). BRAF and NRAS mutations are mostly found in cutaneous melanomas, and KIT mutations are detected in acral and mucosal melanomas. In systemic mastocytosis a KIT D816V mutation is present in almost all cases, in adult-, but not in childhood-onset mastocytosis. This mutation of KIT<sup>D816V</sup> has been found in melanoma, but its involvement is yet not well understood. In some studies, it is shown that KIT<sup>D816V</sup> induces tyrosine phosphorylation of microphthalmia-associated transcription factor (MITF). It forms a triple protein complex formation of KIT, MITF, and SRC family kinases. Activated microphthalmia-associated transcription factor activates genes involved in melanoma proliferation, cell-cycle progression, survival, and also an invasion. Both mast cells and melanocytes need for growth binding of the stem cell factor (SCF) to the KIT receptor. The SCF receptor is expressed in primitive hematopoietic cells and mast cells mostly, but it is also expressed in certain regions of the brain, germs cells, melanocytes and basal cells in the skin, interstitial cells of Cajal. The signalling pathways activated downstream from Kit receptor include MAP kinase pathways, Src kinases, PI3-kinase and phospholipase C and D. Mast cells are producing large subsets of mediators (e.g., EGF, NGF, PDGF, SCF, angiopoietin, heparin, IL-8, VEGF). They are involved in IgE-associated allergic reactions, mostly, but numerous studies have shown the connection between mast cells accumulation and tumour growth – melanoma, Merkel cell carcinoma adenocarcinoma, squamous cell carcinomas, prostate carcinoma, etc. In mastocytosis, RAF is the most frequently mutated kinases, where BRAF V600E mutation occurs in most hairy cell leukaemias (HCL) and half of the malignant melanomas. Thus, although BRAF is commonly mutated, it appears not to be present in SM. The risk-association to other hematologic neoplasms and the risk of cardiovascular disease in mastocytosis is well-established, but also for increased risk of solid cancer as well as thromboembolic morbidity. Mast cells are influencing tumour development and remodelling of tissue, tumour-induced angiogenesis, and shaping of adaptive immune responses to tumours. Mostly presence of mast cells in tumours is associated with poor prognosis, but for prostate cancer and colorectal

cancer is a favorable prognostic factor. The use of kinase inhibitors could improve cancer treatment, but the main problem with this treatment is the second mutation in c-Kit, which changes the binding region of kinase inhibitor, and the result is drug resistance [1], [2], [3], [4], [5], [6].

Melanoma inhibitory activity (MIA) is expressed on mast cells of cutaneous mastocytosis, neurofibroma cells in patients with neurofibromatosis type 1 (NF1) and it is used as a serum marker for malignant melanoma. The function of MIA is in inhibition of apoptosis in melanocytic cells, but the whole mechanisms of expression on mast cells are unknown. Inhibition of the transcription factor, SOX10 reduced MIA expression and promoter activity. This transcriptional factor is important for melanoma development and survival [7], [8].

After exposure to histamine, melanocytes undergo morphological variations and increased activity of tyrosinase. Also, one of the most potent mast cell growth factors- CD-117 binding mast cells growth factor (MFG) stimulates the proliferation of both mast cells and melanocytes.

One of the therapies mostly used for the cutaneous mastocytosis is phototherapy, 311 nm UVB and PUVA and it is well known that UV exposure favour the onset of skin cancers.

The role of estrogens on the development of melanoma and on the exacerbation of the mastocytosis is extremely unknown, but it has been shown in vitro that binding estradiol to estrogen receptor- $\alpha$  on the membrane of mast cells supports the synthesis and release of mast cell mediators [9].

In conclusion, there is an enhanced incidence of melanoma among patients with mastocytosis, especially with systemic mastocytosis, and connection between these two diseases is still not clear. Understanding the influence of mast cells on melanocytes could bring great benefit in threatening the melanoma. New studies are needed.

## References

1. Capo A, Goteri G, Mozzicafreddo G, Serresi S, Giacchetti A. Melanoma and mastocytosis: is really only a coincidence? Clin Exp Dermatol. 2019; 44(1):76-7. <https://doi.org/10.1111/ced.13717> PMID:30178486
2. Molderings GJ, Zienkiewicz T, Homann J, Menzen M, Afrin LB. Risk of solid cancer in patients with mast cell activation syndrome: Results from Germany and USA. F1000Res. 2017; 6:1889. <https://doi.org/10.12688/f1000research.12730.1> PMID:29225779 PMCID:PMC5710302
3. Broesby-Olsen S et al. Risk of solid cancer, cardiovascular disease, anaphylaxis, osteoporosis and fractures in patients with systemic mastocytosis: A nationwide population-based study. Am J Hematol. 2016; 91(11):1069-75. <https://doi.org/10.1002/ajh.24490> PMID:27428296

4. Phung B, et al. KITD816V Induces SRC-Mediated Tyrosine Phosphorylation of MITF and Altered Transcription Program in Melanoma. *Mol Cancer Res*. 2017; 15(9):1265-1274. <https://doi.org/10.1158/1541-7786.MCR-17-0149> PMID:28584020
5. Häggglund H, Sander B, Ahmadi A, Gülen T, Nilsson G. Analysis of V600E BRAF and D816V KIT mutations in systemic mastocytosis. *Med Oncol*. 2014; 31(8):123. <https://doi.org/10.1007/s12032-014-0123-4> PMID:25034364
6. Abbaspour Babaei M, Kamalidehghan B, Saleem M, Huri HZ, Ahmadipour F Receptor tyrosine kinase (c-Kit) inhibitors: a potential therapeutic target in cancer cells. *Drug Des Devel Ther*. 2016; 10:2443-59. <https://doi.org/10.2147/DDDT.S89114> PMID:27536065 PMCID:PMC4975146
7. Ehara Y, Yoshida Y, Tahira M, Yamamoto O. The expression of melanoma inhibitory activity on mast cells in child patients with cutaneous mastocytosis. *Yonago Acta Med*. 2014; 57(3):99-101.
8. Heldin CH, Lennartsson J Structural and functional properties of platelet-derived growth factor and stem cell factor receptors. *Cold Spring Harb Perspect Biol*. 2013; 5(8):a009100. <https://doi.org/10.1101/cshperspect.a009100> PMID:23906712 PMCID:PMC3721287
9. Donati P, Paolino G, Donati M, Panetta C. Cutaneous mastocytosis combined with eruptive melanocytic nevi and melanoma. Coincidence or a linkage in the pathogenesis? *J Dermatol Case Rep*. 2014; 8(3):70-4. <https://doi.org/10.3315/jdcr.2014.1179> PMID:25324908 PMCID:PMC4195503