

## Beta Blockers and Melanoma

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### Abstract

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Understanding the mechanisms of cancer immune-tolerance is one of the most important challenges. Several studies have demonstrated the potential anticarcinogenic effects of beta-blockers, in patients with prostate cancer, breast cancer, and melanoma. At the other side variety of dermatoses may be caused or aggravated by  $\beta$ -blockers-psoriasis, lichen planus-like drug eruptions (LDE), acrocyanosis, alopecia etc. Beta-blockers have been shown to improve the prognosis of melanoma patients significantly. Propranolol inhibits melanoma by downregulating the tumour angiogenesis but also tumour cell proliferation, invasiveness and local immune suppression. Studies showed that only  $\beta_3$ -but, not  $\beta_2$ -adrenoceptors, were up-regulated under hypoxia in peripheral blood mononuclear cells and selectively expressed in immune cell sub-populations including Treg, MDSC, and NK. They increased NK and CD8 number and cytotoxicity. Catecholamines may retard melanoma progression and that  $\beta$ -blockers may have unrecognised potential as a therapeutic intervention for melanoma, in the prevention of the growth of melanoma in all stages and as adjuvant therapy with other targeted and immune therapies for melanoma.

## Introduction

Understanding the mechanisms of cancer immune-tolerance is one of the most important challenges. Melanoma is one of the most aggressive tumours. Metastatic melanoma remains a significant clinical problem, with five-year survival rates of only 15–20%. It is well known that stress-related catecholamines have a role in cancer and  $\beta$ -adrenoceptors.  $\beta_2$ -adrenoceptors have been identified as new targets in treating melanoma.

Recent studies showed  $\beta_3$ -adrenoceptors have a pleiotropic effect on melanoma microenvironment leading to cancer progression, but the mechanisms are poorly

understood.  $\beta$ -Blockers are one of the most widely used therapeutic agents in both cardiac and non-cardiac ailments, but also, have garnered interest amongst dermatologists based on the discovery of their demonstrated and potential effects in disorders such as pyogenic granulomas, vascular malformations, erythematous-telangiectatic rosacea and wound healing.

Several studies have demonstrated the potential anticarcinogenic effects of beta-blockers, in patients with prostate cancer, breast cancer, and melanoma. At the other side variety of dermatoses may be caused or aggravated by  $\beta$ -blockers-psoriasis, lichen planus-like drug eruptions (LDE), acrocyanosis, alopecia etc.

## Discussion

The use of  $\beta$ -blockers in patients with melanoma for the first time was published by De Giorgi et al. A median follow-up of 2.5 years, 34% of patients not using  $\beta$ -blockers had evidence of disease progression, while only 3% of those who used  $\beta$ -blockers (for other diseases) at the time of diagnosis showed melanoma progression.

Psychosocial factors as chronic stress and depression and anxiety are listed as risk factors for cancer onset and progression.

Under conditions of reduced physiological stress, the T cell-dependent anti-tumour immune response is greatly enhanced. These findings suggest that targeting the  $\beta$ AR signalling pathway directly to reduce stress signalling may provide an innovative approach to improve cancer treatment.

Beta-blockers have been shown to improve the prognosis of melanoma patients significantly. Propranolol inhibits melanoma by downregulating the tumour angiogenesis but also tumour cell proliferation, invasiveness and local immune suppression. Calvani et al in their studies showed that only  $\beta_3$ -but not  $\beta_2$ -adrenoceptors, were up-regulated under hypoxia in peripheral blood mononuclear cells and selectively expressed in immune cell sub-populations including Treg, MDSC, and NK. They increased NK and CD8 number and cytotoxicity.

There are several studies with results support previous observation that  $\beta$ -blockers protect patients with thick cutaneous melanoma from disease recurrence and death. In one of them, after only 3 years of treatment, disease progression was observed in 41.2% of the patients in the untreated cohort compared with only 15.8% in the propranolol cohort. Overall survival, although not significant, showed a trend toward decreased mortality in the propranolol group after 3 years of follow-up.

Observational studies have reported the protective effect of  $\beta$ -blockers on the progression of different types of cancers. In total, 25% of them reported previous use of  $\beta$ -blockers that were administered at any time for any other diseases. After a median follow-up of 2.5 years, 34% of the patients in the untreated group showed disease progression. In contrast, only 3% of the patients in the treated group showed progression. After a median follow-up of 8 years and a median duration of  $\beta$ -blocker use of 7.6 years, 45% of the patients in the untreated group and 30% of the patients in the treated group showed disease progression. Notably, in the untreated group, 35% of patients died from melanoma, and only 17% of patients died from melanoma in the treated group. Results of this hospital-based prospective cohort study with a median follow-up of 8 years confirmed our previous results that the use of  $\beta$ -blockers significantly reduced the risk of

Propranolol treatment in the MT/Ret mouse model of melanoma delayed primary tumour growth and metastases development in MT/Ret mice. Propranolol induces a decrease in cell proliferation, and vessel density in the primary tumours and metastases and propranolol significantly reduced the infiltration of myeloid cells, particularly neutrophils, in the primary tumour. Cytotoxic tumour-infiltrating lymphocytes were more frequent in the tumour stroma of treated mice

It is conceivable that a therapeutic approach targeting the beta-adrenergic system could constitute a novel and promising strategy for melanoma treatment.

In one study daily treatment with propranolol slows down tumour development in immunodeficient mice transplanted with human melanoma cells, with the conclusion that non-cardioselective  $\beta$ -blockers affect melanoma progression, and bring first clues about the pathways involved in this antitumor effect.

In conclusion, randomised clinical studies are necessary (the type of  $\beta$ -blocker, characteristics of the tumour, appropriate treatment and efficacy) before  $\beta$ -blockers can be considered a therapeutic option for patients with melanoma. But so far, the observations described suggest that catecholamines may retard melanoma progression and that  $\beta$ -blockers may have unrecognised potential as a therapeutic intervention for melanoma, in the prevention of the growth of melanoma in all stages and as adjuvant therapy with other targeted and immune therapies for melanoma.

## References

1. De Giorgi V, et al. Epidemiology of melanoma: is it still epidemic? What is the role of the sun, sunbeds, Vit D, betablocks, and others? *Dermatol Ther.* 2012; 25(5):392-6. <https://doi.org/10.1111/j.1529-8019.2012.01483.x> PMID:23046017
2. De Giorgi V, Grazzini M, Gandini S, Benemei S, Lotti T, Marchionni N, Geppetti P. Treatment with  $\beta$ -blockers and reduced disease progression in patients with thick melanoma. *Arch Intern Med.* 2011; 171(8):779-81. <https://doi.org/10.1001/archinternmed.2011.131> PMID:21518948
3. De Giorgi V, et al. Epidemiology of melanoma: is it still epidemic? What is the role of the sun, sunbeds, Vit D, betablocks, and others? *Dermatol Ther.* 2012; 25(5):392-6. <https://doi.org/10.1111/j.1529-8019.2012.01483.x> PMID:23046017
4. Calvani M, et al.  $\beta_3$ -Adrenoreceptors Control Mitochondrial Dormancy in Melanoma and Embryonic Stem Cells. *Oxid Med Cell Longev.* 2018. <https://doi.org/10.1155/2018/6816508> PMID:30538804 PMCID:PMC6258109
5. Tatu AL, Elisei AM, Chioncel V, Miulescu M, Nwabudike LC. Immunologic adverse reactions of  $\beta$ -blockers and the skin. *Exp Ther Med.* 2019; 18(2):955-959. <https://doi.org/10.3892/etm.2019.7504> PMID:31384329 PMCID:PMC6639944

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6. Kao J, Luu B. Can propranolol prevent progression of melanoma? *JAAPA*. 2019; 32(6):1-5. <https://doi.org/10.1097/01.JAA.0000558241.84003.91> PMID:31136408
7. Dal Monte M, Calvani M, Cammalleri M, Favre C, Filippi L, Bagnoli P.
8.  $\beta$ -Adrenoceptors as drug targets in melanoma: novel preclinical evidence for a role of  $\beta$ 3-adrenoceptors. *Br J Pharmacol*. 2019; 176(14):2496-2508. <https://doi.org/10.1111/bph.14552>
9. Sang Y, Deng Y. Current insights into the epigenetic mechanisms of skin cancer. *Dermatol Ther*. 2019; 32(4):e12964. <https://doi.org/10.1111/dth.12964> PMID:31081988
10. Mervis JS, McGee JS. Epigenetic therapy and dermatologic disease: moving beyond CTCL. *J Dermatolog Treat*. 2019; 30(1):68-73. <https://doi.org/10.1080/09546634.2018.1473550> PMID:29726727