

correlated with high apoptotic index and tumour cell proliferation by Ki-67 expression.

As described in this work, cell cycle regulation seems to be of major importance in cancer, including malignant melanoma. Reduced expression and reduced function of the tumour suppressor p16 is a common event in advanced melanomas, although alterations of the CDKN2A gene often are not detected. The mechanisms leading to p16 inactivation in malignant melanoma are still largely unresolved, and BMI-1 is unlikely to be a major up-stream regulator of p16. Future studies should therefore pursue the regulatory mechanisms of p16 inactivation often observed in advanced malignant melanoma. Ongoing studies are focusing on the Cdc6 protein, which is proposed to be a repressor of the CDKN2A/INK4 locus.

During the last years, the concept of cancer being dependent on a single cell or a few cells with stem-cell like properties has emerged. Recognition of these cancer stem cells in tumours may lead to a new therapeutic era, since eradication of tumour stem cells theoretically would terminate further tumour growth and renewal. There is a need for continued search for “signatures” of malignant melanoma stem cells, and further exploration of the Polycomb group of genes is justified. In addition, the relationship between stem cell phenotypes and prognosis should be further explored.

Tumour hypoxia, angiogenesis, and tumour progression are intimately connected. Necrosis and apoptosis are considered morphological features of tumour hypoxia, whereas changes in gene expression and tumour cell properties are less well described. In the future, a discovery driven approach should be combined with hypothesis-based studies, to better identify tumours with different prognostic profiles for optimal targeted therapy.

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Erythromelalgia and the Shunt Hypothesis

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Cato Mørk has defended his thesis on erythromelalgia for the degree of dr.med. at University of Oslo.



Erythromelalgia is characterized by red, hot and painful extremities. Cato Mørk's doctoral thesis is based on four studies on this rare condition. Dr Mørk has recently been appointed Professor of Dermatology at the University of Oslo and Senior Consultant at Rikshospitalet.

Erythromelalgia is a rare disease characterized by red, hot and painful extremities. Local skin cooling provides relief.

Warmth, exercise and dependency of the extremity intensify the discomfort (1). Clinical observations and pathophysiological findings are compatible with microvascular arteriovenous shunting of blood as a final common pathway of pathogenesis of erythromelalgia in affected skin. This shunt hypothesis postulates that available blood is maldistributed. An insufficient proportion of blood is directed through nutritional capillaries, leading to skin hypoxia, while a large proportion

of blood is shunted through microvascular anatomical or functional arteriovenous anastomoses. The skin hypoxia induces arteriolar dilatation and hyperaemia, resulting in elevated skin temperature and accelerated metabolism. Because the hyperaemic perfusion is still maldistributed, the hypoxia is not revealed. This vicious cycle may be triggered by different mechanisms related to haemorrheological problems, defects in prostaglandin metabolism, dysfunction of endothelial cells or the autonomic nervous system.

The aim of the studies (2–5) was to challenge the shunt hypothesis, to characterize the mechanisms underlying the vascular dysfunction in erythromelalgia, and to test if therapy, based on this understanding of the pathogenesis, would improve clinical and objective outcome measures in patients with erythromelalgia.

Patients were selected from a database of erythromelalgia patients ($n = 160$) built up over nearly 20 years. The patients were characterized by demographic and clinical variables (cooling and pain scores, global assessment). Skin perfusion was assessed using laser Doppler flowmetry (LDF), laser Doppler perfusion imaging (LDPI) and computer-assisted video microscopy (CAVM). LDPI assesses global (thermoregulatory and nutritive) skin perfusion; CAVM evaluates skin capillary morphology. Perfusion was assessed following vasoconstrictory and vasodilatory stimuli to characterize central and local neurogenic reflexes as well as vascular smooth muscle and vascular endothelial cell function and following central body heating to provoke erythromelalgia symptoms in patients and healthy controls. In a double-blind, crossover, placebo-controlled clinical trial, erythromelalgia patients were treated with misoprostol, a prostaglandin E1 analogue with vasodilatory and thrombocytic inhibitory effects.

In patients with erythromelalgia, LDF-assessed skin microvascular perfusion was significantly reduced during basal conditions. Vasoconstrictor responses involving central sympathetic reflexes were attenuated in affected skin. Central body heating induced a significant increase in LDPI-assessed perfusion and reduction in capillary density in affected erythromelalgia (EM) skin containing many anatomical arteriovenous shunts, compared with asymptomatic patients and controls. In areas with no or few shunts, the groups did not differ. We demonstrated beneficial clinical effects of misoprostol and redistribution in skin microcirculation in favour of nutritive perfusion.

In conclusion, increased thermoregulatory flow and decreased capillary density during erythromelalgia attacks, as



Fig. Professor Terence Ryan, University of Oxford, and Professor Knut Kvernebo. Professor Knut Kvernebo was the main supervisor for this research, which was carried out in co-operation with the University of Linköping, Sweden. Professor Terence Ryan, University of Oxford, UK (1st opponent), Professor John Tooke, Peninsula Medical School, UK (2nd opponent), and Professor Knut Gjesdal, University of Oslo, Norway, were members of the doctoral thesis committee.

well as clinical improvement and redistribution of the skin microcirculation in favour of the nutritive perfusion after misoprostol treatment, give support to the shunt hypothesis. Erythromelalgia was associated with neuropathy, which may be one underlying mechanism for the disturbance in the vascular dynamics. Vasculopathy with hypoxia may also cause neuropathy.

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