

The Role of Hypoxia-induced Macroautophagy in Melanomagenesis

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Cutaneous Malignant Melanoma (CMM), the most lethal type of skin cancer, is largely refractory to existing therapies and has a very poor prognosis, urging better understanding and new therapeutic approaches for this devastating disease. Hypoxia is an important micro-environmental factor for melanocytes and primary CMM (residing in the mildly hypoxic basal layers of the epidermis) as well as within the solid CMM tumor (due to insufficient as well as malfunctioning blood supply). Hypoxia has emerged as a synergistic factor in melanocyte transformation (Bedogni *et al* 2005) and CMM therapy resistance (Sanna *et al* 1994). Decreased availability of oxygen is a cellular stress known to stimulate autophagy, a conserved lysosomal pathway for the recycling of cytoplasmic materials, including proteins and damaged organelles. The role of this catabolic process in carcinogenesis remains largely unclear and both a tumor suppressor as well as a tumor promoter role have been reported.

In this study, we examined the relevance of skin mild hypoxic status (1.5-5% O₂) in autophagy stimulation and the role played by this process in melanomagenesis. We found that skin mild hypoxia confers a growth advantage to both melanocytes and CMM cell lines representing different melanoma progression stages, which was associated with the induction of autophagy. However, the basal autophagic flux was substantially higher in melanoma cells than in the melanocytes, suggesting that cancer cells may depend more pronouncedly on this catabolic process to cope with stress. Dissection of the molecular pathways revealed mitochondrial superoxide generation, PHD2, HIF-1 α and BNIP3 as the key molecular players involved in autophagy induction as well as the selective removal of damaged mitochondria through autophagy (mitophagy) under hypoxia. Intriguingly, blockage of autophagy (using pharmacologic inhibitors or siRNA-mediated knock down) under hypoxia inhibited growth and induced apoptosis in CMM cell lines, but not in melanocytes. The induction of apoptosis in the cancer cell lines was preceded by a disruption of the mitochondrial network, mitochondrial swelling and an increase in mitochondrial ROS, leading eventually to mitochondrial membrane permeabilisation. All together, these data suggest that mild hypoxia-driven mitophagy confers stress tolerance and increases CMM fitness under metabolic stress conditions while being dispensable to sustain the survival of normal melanocytes. This notion, which our ongoing *in vivo* experiments appear to support, may open a window for new therapeutic approaches in CMM.

References:

Bedogni B *et al*. The hypoxic microenvironment of the skin contributes to Akt-mediated melanocyte transformation. *Cancer Cell*. 2005 Dec;8(6):443-54.

Sanna K *et al*. Hypoxia-induced resistance to doxorubicin and methotrexate in human melanoma cell lines *in vitro*. *Int J Cancer*. 1994 Jul 15;58(2):258-62.