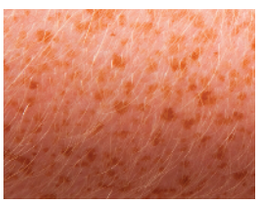
Melanoma

Major finding: Pheomelanin promotes melanoma in the red hair/fair skin background independent of UV radiation.

Mechanism: Pheomelanin synthesis due to *Mc1r* polymorphisms promotes oxidative damage in the skin.

Impact: Other preventive strategies may be necessary in addition to protection from UV radiation.

RED HAIR/FAIR SKIN PIGMENTATION DIRECTLY ENHANCES MELANOMA INCIDENCE



The red hair/fair skin phenotype is associated with increased risk of melanoma due to polymorphisms in the *melanocortin 1 receptor* (*MC1R*) gene. These polymorphisms result in decreased activity of the MC1R cyclic AMP–stimulating G-protein–coupled receptor and production of the red/yellow pheomelanin pigment, which exhibits impaired shielding against UV radiation compared with the black/brown pigment, eumelanin. Mitra and colleagues used mouse pigmentation phenotype models that mimic dark-skinned and red hair/fair skin individuals together with inducible, melanocyte-specific oncogenic BRAF V600E expression to determine whether pigment pathways also contribute to melanomagenesis independent of UV radiation. Elevated pheomelanin production in red–$Mc1r^{e/e}$ mice, which carry an inactivating mutation in *Mc1r*, was sufficient to enhance melanoma formation in the absence of environmental stressors such as UV radiation, compared with the low melanoma incidence in wild-type black mice and albino mice that lack all pigment synthesis. Melanomas from each background were histologically similar, amelanotic dermal tumors that exhibited expression of standard melanoma markers, local invasion, the ability to respond to melanocytic differentiation signals, and a dependence on oncogenic BRAF activity. Intriguingly, genetic ablation of pigment synthesis in $Mc1r^{e/e}$ mice via introduction of the mutant *tyrosinase* albino allele into this background protected red mice from melanoma, suggesting that pheomelanin or the pathway leading to its synthesis directly promotes tumor formation. This increased melanoma risk is likely driven by augmented reactive oxygen species–mediated damage, as increased oxidative DNA and lipid damage were observed in the skin of red–$Mc1r^{e/e}$ mice compared with albino–$Mc1r^{e/e}$ animals. These findings suggest that the intrinsic tumor-promoting function of pheomelanin cooperates with UV radiation–mediated effects to enhance melanoma risk and underscore the need for additional protective strategies in individuals with red hair and fair skin. ■

Mitra D, Luo X, Morgan A, Wang J, Hoang MP, Lo J, et al. An ultraviolet-radiation-independent pathway to melanoma carcinogenesis in the red hair/fair skin background. Nature 2012;491:449–53.

Hypoxia

Major finding: HIF2α activates mTORC1 via SLC7A5 to promote proliferation in tumors lacking VHL.

Mechanism: HIF2α induces *Slc7a5* transcription to sustain mTORC1 activity when amino acids are limited.

Impact: In contrast to HIF1α and other oxygen-sensing pathways, HIF2α promotes mTORC1 activation.

AN AMINO ACID CARRIER LINKS THE HIF2α PATHWAY AND mTORC1 REGULATION

Hypoxia-inducible factor 1α (HIF1α) activation and some HIF-independent pathways suppress proliferation and protein translation under hypoxic stress by inhibiting mTOR complex 1 (mTORC1), which regulates cell growth in response to oxygen deprivation. In contrast, HIF2α stimulates proliferation in tissues such as the liver and enhances the growth of von Hippel-Lindau (VHL)–deficient renal cell carcinoma (RCC). To investigate the mechanisms underlying the tumor-promoting properties of HIF2α, Elorza and colleagues tested whether HIF2α differentially regulates mTORC1 activity. Under conditions of reduced amino acid availability similar to those in the intratumoral microenvironment, expression of HIF2α but not HIF1α resulted in phosphorylation of eukaryotic translation initiation factor 4E binding protein 1 (4EBP1) and ribosomal protein S6 (rpS6), indicative of increased mTORC1 activity. This effect was dependent on HIF2α-mediated transcriptional induction of *solute carrier family 7* (*amino acid transporter light chain, L system*) *, member 5* (*Slc7a5*), which encodes for an amino acid carrier necessary for mTORC1 activity. SLC7A5-triggered mTORC1 activation augmented cell proliferation in low amino acid conditions and promoted the growth of VHL-deficient xenograft tumors; increased SLC7A5 expression was also detected in human RCC samples, supporting a critical role for this pathway in HIF2α-driven tumor cell proliferation. In addition, HIF2α expression was specifically required for mTORC1 activation induced by hypoxia or *Vhl* ablation in the lung, which expresses high levels of *Hif2a*, and in *Vhl*-deficient liver tissue, as loss of *Hif2a* impaired *Slc7a5* upregulation and downstream phosphorylation of 4EBP1 and rpS6. These results identify hypoxia and HIF2α as important activators of mTORC1 under certain physiologic conditions and provide insight into the molecular mechanism by which HIF2α promotes tumorigenesis. ■

Elorza A, Soro-Arnáiz I, Meléndez-Rodríguez F , Rodríguez-Vaello V, Marsboom G, de Cárcer G, et al. HIF2α acts as an mTORC1 activator through the amino acid carrier SLC7A5. Mol Cell 2012 Oct 24 [Epub ahead of print].