Preventing melanoma development by manipulating pigment levels.

Melanoma is a deadly skin cancer that is diagnosed in more than 75,000 people and estimated to cause 9710 deaths per year in the United States alone.(1) Melanoma arises from mutations in melanocytes, the pigment-producing cells in the skin. There are two main types of pigments synthesized by melanocytes, pheomelanin and eumelanin, and there are many polymorphisms that lead to different ratios of these pigments in humans. (4, Figure 1)

It has been observed that the main drivers of melanoma development act through UV-dependent and UV-independent pathways. In the UV-independent pathway, it is the pheomelanin pigment synthesis pathway in particular that appears to promote the development of melanoma.(2) Researchers have found that the presence of eumelanin is associated with greater protection from UV damage and lowered risk of melanoma development. Recent studies suggest that when eumelanin and pheomelanin are both present in melanocytes, eumelanin can encase pheomelanin and pheomelanin's intermediates in its synthesis pathway to protect melanocytes from the toxicity attributed to the pheomelanin synthesis pathway.(1) However, the mechanisms through which the pheomelanin synthesis pathway and the ratio of pheomelanin to eumelanin affect melanoma progression remain unclear.

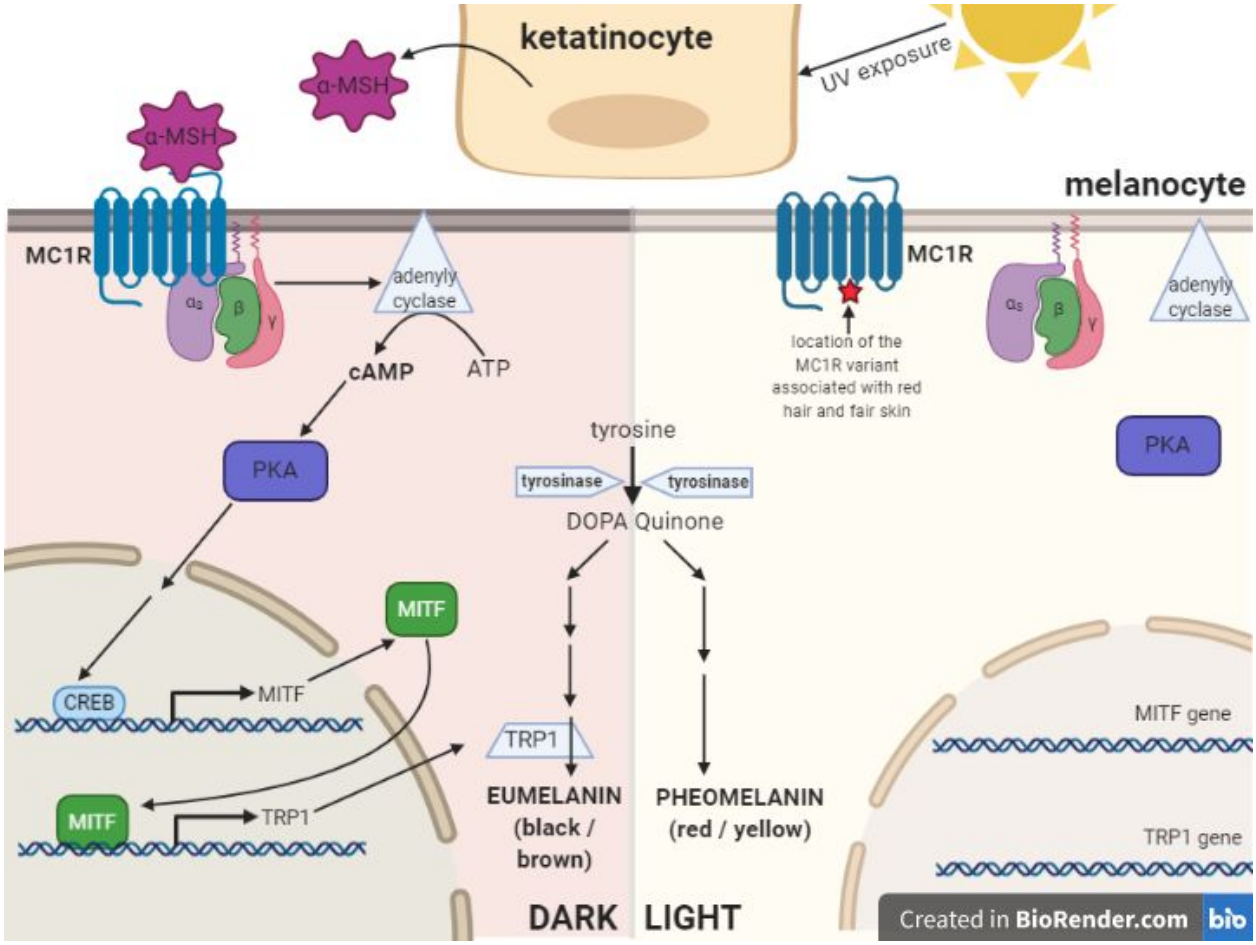
Hence, my research question is how exactly does the ratio of eumelanin to pheomelanin affect the development of melanoma and can it be manipulated to lower melanoma risk? My hypothesis is that if you increase the ratio of eumelanin to pheomelanin, then the amount of oxidative DNA damage in melanocytes will decrease and the development of melanoma will slow because the eumelanin will encase the pheomelanin and protect melanocytes from any effects pheomelanin and its intermediates may have on amplifying the level of reactive oxygen species in the cell. My goal is to identify an ideal ratio and technique to employ eumelanin to lower the risk for melanoma development in individuals with naturally high levels of pheomelanin.

To investigate my hypothesis, I plan to use *in vivo* BRAF V600E mice models. These mice contain a mutation in their BRAF gene, a gene that is mutated in around 30% of melanomas. It has been experimentally suggested that mutating the BRAF gene alone is not sufficient to cause melanoma development but is a good starting point to analyze if additional mutations caused by pheomelanin and eumelanin would be enough to cause and accelerate melanoma development. (2) To change the ratio of pheomelanin to eumelanin in the mice, I will take two approaches. First, I will directly inject eumelanin into BRAF V600E mice with an inactivating mutation in their MC1R gene (this simulates the polymorphisms that cause some humans to produce pheomelanin) at different concentrations relative to the natural level of pheomelanin. Second, I will introduce repressors of varying binding affinities to the MC1R gene to control the level of pheomelanin production. From these approaches, I will measure melanoma development in two ways. To measure oxidative DNA damage, I will use a liquid chromatography-tandem mass spectrometric method to measure the levels of ROS-mediated cyclopurines, 8,5'-cyclo-2'-deoxyadenosine and 8,5'-cyclo-2'-deoxyguanosine, in DNA isolated from melanocytes on the skin of the mice. (2, 5) To measure melanoma development, I will measure the size and observe the histology of tumors that appear on the mice over a period of 8 months.

I anticipate that mice with higher levels of eumelanin to pheomelanin, regardless of the mechanism of manipulating the pigment ratio, will have decreased melanoma development and lower levels of oxidative DNA damage.

In conclusion, manipulation of eumelanin and pheomelanin levels may be a method through which we can lower the risk of red-hair/fair-skin individuals to melanoma development before it becomes too late, and they reach a stage of terminal metastatic melanoma. The elucidation of this pathway could be revolutionary for the field of melanoma research and could pave the way for similar mechanisms in the treatment and prevention of other cancers as well.

Figures:
1.(3)



References:

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