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Development of the MC1R selective ligands for the melanoma prevention

Minying Cai, Yang Zhou, Saghar Mowlazadeh Haghighi, Ioanna Zoi, Victor Hruby, Jixun Dai

University of Arizona, United States

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Introduction

The incidence of melanoma, the most commonly fatal form of skin cancer, is increasing faster than any other potentially preventable cancer in the United States [1]. Estimates for 2016 are that 76,100 invasive melanomas will be diagnosed in the United States and that melanoma could claim 9710 lives.[2] Melanoma is the fifth most common cancer in men and seventh in women in the United States. Melanoma lesions generally evolve in a stepwise fashion, beginning as a typical nevi and progressing to melanoma in situ, *via* a radial growth, vertical growth malignant melanoma and metastasis. Although pre-cancerous nevi are easy to diagnose and curable with resection, they often go unnoticed and the majority of melanoma patients present with advanced disease. Once the disease is metastatic it is uniformly fatal with a median survival rate of only 4-6 months. Many approaches to treatment have been explored including radiotherapy, chemotherapy, immunotherapy and hormonal therapy, with minimal success. Therefore, developing melanoma prevention agent is becoming critical important. Normally, people with lighter skin color, light hair and light eyes are more at risk, because they have less melanin in their skin to protect them. Current efforts to prevent UV damage miss leading people exposed more under the sun, which in many cases leads to melanoma and other skin cancers. This proposal will provide a new way of melanoma prevention.

Results

Melanoma progression is associated with altered expression of cell surface proteins, including adhesion proteins and receptors.[3-6] It is estimated that over 80% of malignant melanomas express higher levels of melanocyte stimulating hormone (α-MSH) receptors, human melanocortin 1 receptor (hMC1R). The hMC1R is associated with skin pigmentation. Upon activation, the hMC1R in melanocyte and keratinocytes will form the pigmentation to block the UV radiation to prevent skin damage. The endogenous hMC1R ligands, α, β , γ-stimulate hormone, (α, β , γ-MSH) are derived from the POMC gene,[7] a part of a primordial system which is critical for survival. Endogenous MSH peptides exist *in vivo* and therefore, developing MSH based melanoma therapeutic agents are unlikely to run into issues of rejection and drug resistance. Several previous studies have investigated tumor targeting with non-selective radiolabeled MSH analogs, resulting in high quality images with sharp contrast. However, these studies all lack specificity. A motivation for the current study is developing highly selective hMC1R melanotropins and conjugates to reach the highest specificity to melanoma cells. To date, several compound of our discovery are already in Phase 2/3 clinical trials; the linear peptide [Nle^4, D-Phe^7]α-melanocyte (MT-1) stimulating hormone (NDP-α-MSH, ScenesseTM) has advanced to the status of a marketed drug (for congenital erythropoietic protoporphyria) in Europe and skin disorder prevention agent in Australia. However, NDP-α-MSH (MTI-1) represents a non-selective MCR agonist.[8] Nonselective MSH analogues, such as MTI/MTII, as a single target for drug delivery and imaging are problematic as hMCRs are also highly expressed in a number of normal tissues, including in the colon and the lung. Hence, coupling the target of a highly selective MC1R ligand to melanoma cells should provide improved specificity for earlier diagnosis, treatment and ultimately the prevention of melanoma.

We have been very successful in developing selective hMC1R ligands in the past twenty years. Recently, using NMR and computational aid drug design combined with chimeric receptor studies we can design more bioavailable and druggble selective hMC1R ligands rationally. As an example, we successfully developed only natural amino acid made peptide, [Leu3, Leu7, Phe8]-γ-MSH-NH_2, which is a potent selective hMC1R agonist with 24nM binding affinity and 4.5 nM functional activity[9] (Figure 1 .) and many other hMC1R selective agonists such as Ac-His-DPhe(4-CF_3)-Nle-Trp-NH_2 which are more druggable and bioavailable with 339nM binding affinity and 10nM functional activity.[10] NMR structure demonstrated that Ac-His-DPhe(4-CF_3)-Nle-Trp-NH_2 is β -turn structure. *In vivo* studies demonstrated these peptides can cause immediately pigmentation. The natural skin color can be resumed less than 20 hours. The high selectivity of peptides [Leu^3, Leu^7, Phe^8]-

-γ-MSH-NH_2 and Ac-His-DPhe(4-CF_3)-Nle-Trp-NH_2 for the hMC1R, and shorter half-life provides a safer and reduced side-effect agent for the prevention of melanoma skin cancer. Since binding affinity of [Leu^3, Leu^7, Phe^8]-γ-MSH-NH_2 is 20 times than peptide Ac-His-DPhe(4-CF_3)-Nle-Trp-NH_2 the pigmentation is stronger. This research will be more applicable and will be benefit for most people for skin cancer prevention.

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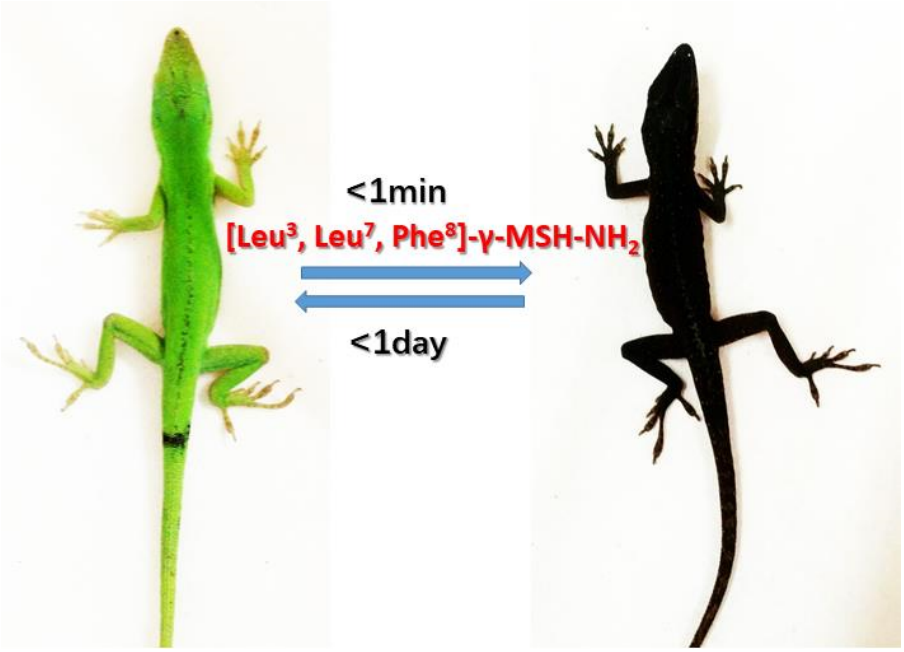

Figure 1: Computational aid drug design combined with chimeric melanocortin receptor studies led to selective hMC1R agonist: [Leu3, Leu7, Phe8]-γ-MSH-NH_2 with functional activity of pigmentation.[9]

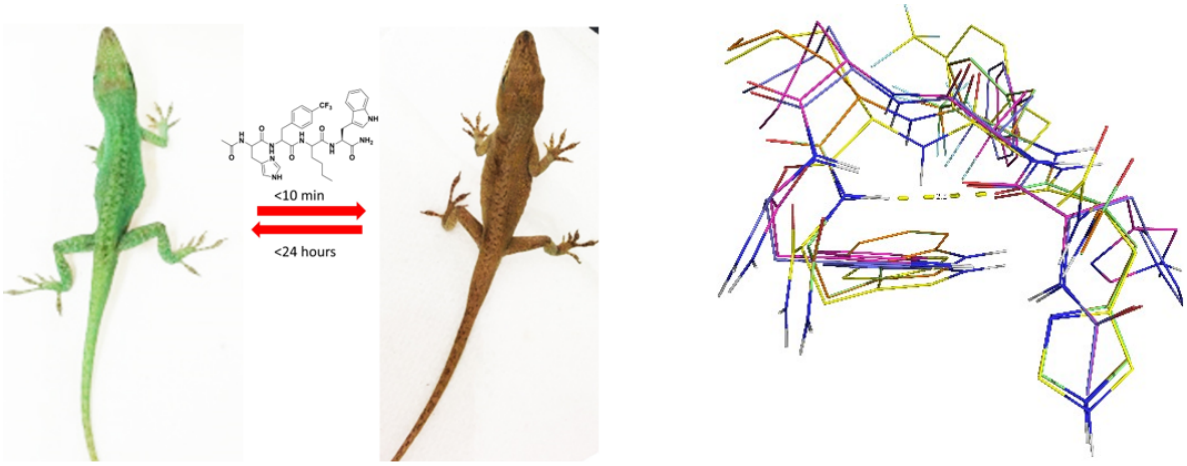

Figure 2: Conformational studies of pharmacophore of MSHs led to selective hMC1R agonist Ac-His-DPhe(4-CF3)-Nle-Trp-NH_2 with functional activity of pigmentation.[10]

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