Treatment with Modified Heat Shock Protein Repigments Vitiligo Lesions in Sinclair Swine

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HSP70i is secreted by stressed melanocytes, is associated with human vitiligo lesions, and functionally contributes to a mouse model of vitiligo. Henning et al. report that treatment with a modified version of the protein reversed depigmentation in Sinclair swine, a useful animal model of vitiligo. These studies provide the rationale for testing in human studies.


Henning et al. (2018) report successful treatment of vitiligo in Sinclair swine, an animal model of vitiligo that shares features of human disease (Essien and Harris, 2014). The treatment is through delivery of a DNA plasmid encoding a modified HSP70i. The rationale for this approach is based on previous work that reported induction of HSP70i in human vitiligo lesions, by stressed melanocytes, and by melanocytes exposed to vitiligo-inducing chemicals; HSP70i can also stimulate plasmacytoid dendritic cells to produce proinflammatory cytokines (Abdou et al., 2013; Jacquemin et al., 2017; Kroll et al., 2005; Mosenson et al., 2014). Mechanistic studies in mice showed that HSP70i is required for vitiligo, that its overexpression worsens vitiligo, and that a mutant HSP70i molecule (HSP70iQ435A) could prevent disease (Denman et al., 2008; Mosenson et al., 2011).

The proposed mechanism of action by which HSP70i contributes to vitiligo is through its ability to stimulate innate immunity, which results in loss of tolerance toward melanocytes in vitiligo (figure 1). Henning et al. (2018) describe a method to counteract this proinflammatory signal through DNA jet injection of a plasmid encoding HSP70iQ435A, which was previously shown to antagonize the function of the endogenous HSP70i and prevent disease in a mouse model of vitiligo. They found that treatment of perilesional skin successfully suppressed nuclear HSP70i expression in treated skin and that four weekly treatments for a duration of four weeks was sufficient to induce reversal of depigmentation as measured by a reduction in the surface area of depigmented lesions. They additionally report that repigmentation persisted after treatment cessation and that lesions continued to further repigment up to 6 months after treatment cessation. Thus, the results of this treatment may be long lasting, consistent with the investigators’ hypothesis that this approach re-establishes natural tolerance to initiate disease in skin by counteracting a critical vitiligo-initiating signal.

Existing vitiligo treatments require some form of continuous treatment or maintenance therapy because relapse frequently occurs after stopping treatment. Reportedly, 40% of vitiligo patients experience relapse of vitiligo within 1 year of stopping any combination of conventional treatments, including narrow band UVB, topical calcineurin inhibitors, and topical corticosteroids (Cavalié et al., 2015). This appears to include emerging treatments such as JAK inhibitors as well. Our previous observations in a patient treated with ruxolitinib showed that the patient’s depigmentation returned within 12 weeks of stopping treatment, and similar relapse was described in a patient treated with tofacitinib (Harris et al., 2016; Liu et al., 2017). It would be interesting to determine in future studies whether the lasting improvement observed in the Sinclair model correlates with a long half-life of the plasmid or if tolerance persists after the plasmid has been cleared from the tissue.

Local treatment with HSP70iQ435A also induced repigmentation of distant, untreated lesions, suggesting that the local treatment had a systemic effect, which is not characteristic of current topical treatments. This is analogous but conversely related to clinical experience with chemical-induced vitiligo and chemical depigmentation therapy for vitiligo, in which depigmentation occurs both at the site of topical exposure and at distant, untreated sites (Harris, 2017). Considering that chemicals known to trigger vitiligo increase HSP70i expression—and that HSP70iQ435A counteracts HSP70i signaling, these opposing observations strongly suggest that local skin HSP70i can influence systemic immune tolerance for melanocytes in vitiligo (Kroll et al., 2005).

Unaltered susceptibility to melanoma by HSP70iQ435A within this model is encouraging as it relates to its therapeutic potential. Although vitiligo patients are reportedly less susceptible to melanoma (Rodrigues, 2017), they still have some risk of developing this life-threatening cancer, and moderate concern exists about whether inducing tolerance to melanocytes would increase the incidence of melanoma. Because human melanomas are heterogeneous and have variable prognoses and responses to treatment, it will be important to identify the impact of HSP70iQ435A on overall melanoma incidence. However, these early results are promising.
The successful treatment of vitiligo by Henning et al. (2018) represents a significant step toward the ultimate goal of permanently restoring proper immune tolerance to melanocytes in vitiligo patients. These findings show promise for HSP70iQ435A as a new vitiligo treatment, and clinical studies will be necessary to investigate the safety and efficacy of this treatment in human subjects. The feasibility of introducing recombinant DNA into human skin using an air jet injector delivery system will also need to be considered when designing future clinical trials in humans, advancing along the regulatory pathway for the treatment, and preparing for the clinical implementation of this therapy. Importantly, the pUMVC3 plasmid vector used to introduce HSP70iQ435A into the skin has been approved for use in several clinical trials testing new cancer treatments, which may make it easier to advance along regulatory pathways; although, its use for a nonlethal disease may be an additional hurdle. In light of this concern, it might also be worthwhile to test other methods of targeting HSP70i in vitiligo that can be more easily translated to human treatments, such as blocking the signaling pathway with antibodies or small molecules. In any case, this new study opens the door to a new therapeutic strategy for vitiligo, which provides more options for the future management of vitiligo patients.

CONFLICT OF INTEREST
The authors state no conflict of interest.

REFERENCES