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Vitiligo Induction Methods: A Review Update

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a) Abstract:
Vitiligo is a disease that results in the decrease of melanin content from our skin resulting in patches that grow bigger in time as they progress. The part that gets affected is the skin as it is very prone to the external threshold. These can be further moved to other parts of body starting from the oral cavity and then spreading to other parts. They are generally linked with pathophysiological disorders and in some cases can worsen with mental conditions as there is a hindrance and less acceptability. They can be autoimmune or can be chemically induced against the cells of melanocytes which is the responsible agent of the same. In this study, the chemical model monobenzone-induced vitiligo (MBEH) was used. The Monobenzone concentration below 20% it not cause depigmentation skin but when concentration is above 20- 40% it causes depigmentation skin and The HQ concentration used below 2% it not cause vitiligo but when we use HQ concentration above 2% it causes vitiligo skin. Hydrogen peroxide 3% concentration is used for wound healing. It is quite common that these are the factors leading to the occurrence of the diseases and synergistic with stress-induced mechanisms. So this article will summarize all the concern factors leading to vitiligo and its treatment regimes.
b) Key Word: Monobenzone, Transgenic mouse, C57BL/6mice, Hybrid Mice.
c) Running Title: Vitiligo Models

INTRODUCTION

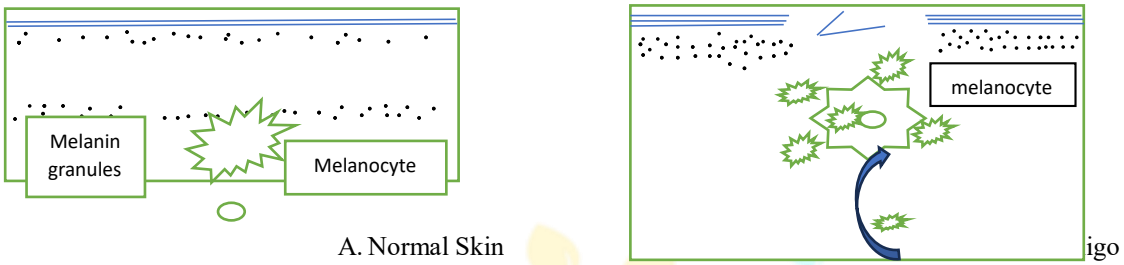
A condition that results in patchy skin color loss. According to theory, vitiligo develops when pigment-producing cells die or stop functioning. Skin discoloration can occur anywhere on the body, including the mouth, eyes, and hair. Individuals with darker skin tones may see it more prominently. Globally, vitiligo affects over 1% of the population.

While treatment can help the skin seem better, the illness cannot be cured by it. An autoimmune condition called vitiligo is chronic (long-lasting), resulting in regions of skin losing color and pigmentation. This happens when the skin's pigment-producing cells, known as melanocytes, are attacked and destroyed, turning the skin a pale white color. The skin ailment known as vitiligo (pronounced "vit-il-EYE-go") results in the loss of pigmentation or color in the skin. Your skin will appear whiter or lighter than it actually is as a result of this. Pigment-losing skin areas are referred to as spots if they are greater than 1cm in width or macules if they are smaller than 1cm . Your hair may turn silver or white in areas of your body where you have vitiligo.

Equal numbers of both men and women are afflicted, About 50% of those affected have vitiligo prior to turning 20. Other autoimmune conditions include thyroiditis, type 1 diabetes, Patients and their family are more likely to get alopecia areata, Addison's disease, and pernicious anemia. Though it can affect any portion of the skin, depigmentation most frequently impacts the hands, feet, and face, genitalia. Epidermal melanocytes are absent from affected skin, although hair follicles in the lesioned skin are frequently preserved, most likely as a result of the hair follicle's immunological privilege. Repigmentation of the skin follows a successful course of treatment; this pigmentation starts in the area surrounding the hair follicles and most likely stems from reservoirs of melanocyte stem cells housed within the follicle and protected.(Xing et al., 2016)·(Glassman, 2011)The absence of melanocytes in vitiligo's depigmenting patches had to be established before researchers could look into the disease's origin. The removal of differentiated melanocytes from the skin of vitiligo lesions was aided by using antibodies for immunostaining against various molecules on melanocytes. Furthermore, c-KIT labeling for un-differentiated melanocyte stem cell show that the skin of vitiligo lesions lacked melanocyte progenitors.(Steel et al., 1992)

It's unclear exactly what pathophysiology vitiligo has. Regarding the pathophysiology of vitiligo, there are a number of main theories:
(i) Autoimmune pathogenesis is a well-established and widely accepted theory.

(ii) According to the neural hypothesis, neurochemicals released by nerve endings have the ability to harm melanocytes or decrease the production of melanin.(Choi et al., 2014)
(iii) The biochemical theory postulates that the degeneration of melanocytes is caused by the buildup of harmful intermediate metabolites of melanin formation (Kemp et al., 2001), a compromised immune system against free radicals (Pawelek et al., 1980), and an excess of hydrogen peroxide (H2O2) (Nordlund, 1982). Other theories suggest that Melanocyte growth factor deficiency, structural and functional anomalies in melanocytes, and hereditary variables all impact the depigmentation process.
These data strongly imply that vitiligo and melanoma immunology share melanocyte-specific immune responses. The pathophysiology of vitiligo is caused by a multitude of reasons, including abnormalities, autoimmunity, environmental stressors, internal melanocytes, or genetic factors that impact on the components. [3,(Laddha et al., 2013; Richmond et al., 2013)]



A. Normal Skin igo

Fig.1: Ros Play a crucial role in the start of vitiligo. (A) Vitiligo is a discolouration of skin disorder it caused by disturbances of melanocytes that are attack by Immunity.

Animal Models of Vitiligo

Caused vitiligo by stressing melanocytes

A chemical analog of tyrosine that is clinically significant, monobenzone causes pro-inflammatory signals, worsens depigmentation in vitiligo patients and causes cellular stress in melanocytes.(Passeron & Ortonne, 2012) Four-week-old mice were given monobenzone to shaved abdomens; hair decolouration started at the cure area and eventually extended to other areas like the tail and ear. Following treatment, CD8ξ T cells penetrate the afflicted skin. In RAG-deficient mice, the same treatment led to hair decolouration at the cure area yet rarely at other locations.(Zhu et al., 2013a) The results imply one localized depigmentation at the application site may be caused by direct monobenzone toxicity, but that depigmentation cannot spread to other locations without an adaptive immune response. This model could be useful in figuring out how stress caused by monobenzone triggers the immune system in cases of vitiligo.

Immunization-induced vitiligo

One group created recombinant vaccine viruses (rVVs) that indicate distinct melanocyte irritant in an attempt to trigger immune responses against melanoma. Using the germ to immunize. The C57Bl6 mice, they discovered that infection with rVVs. Which expresses person TRP1, caused 80% of the animals to have depigmented hair follicles while leaving the brain and eyes pigmentation intact. This idea states that autoantibodies specific to melanocytes develop at the same time as depigmentation, which depends on CD4+ T cells instead of CD8+ T cells.(Overwijk et al., 1999) One benefit of Immunization-induced vitiligo is the role of internal host immuno cells in decolouration; this allows the study of host immunity factors that contribute to the loss of melanocytes.
Using a gene gun, DNA plasmids expressing the human TRP2 melanocyte antigen were injected directly into the mice's skin. [13–14] A gene pistol that runs on carbon dioxide is used to deliver the gold-coated DNA microparticles into the skin. Next, plasmid-transformed skin cells express tyrosinase-related protein 2. Growing hairs get depigmented after treatment; this is reliant on CD8+ T-cells or their showing of perforin.(Bowne et al., 1999)
Additionally, antibodies directed at peopleTRP2 were generated. (Steitz et al., 2004) In contrast to vaccines missing HSP70i, studies employing plasmids delivered by gene gun that encoded people TRP-2 and people HSP70i enhanced decolouration in use mice.(Denman et al., 2008) It appears from this discovery that HSP70i has a role in depigmentation. This connects functional immunological responses unique to melanocytes in vitiligo to HSP70i produced by stressed melanocytes. A later investigation found that the mutant form of HSP70i inhibited the production of disease in this model and was unable to cause disease. (Mosenson et al., 2013) This method works well for investigating how adjuvants, such HSP70i, affect the onset and progression of disease since it is simple to introduce plasmids encoding essential proteins during immunization.

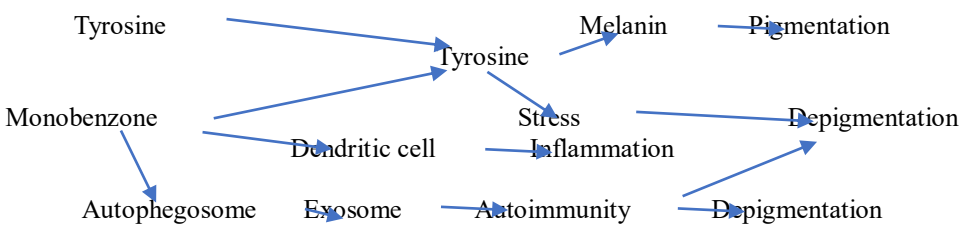


Fig2: The mechanisms of chemical vitiligo.

Chemical Vitiligo

It was thought that chemically induced skin depigmentation posed a risk to workers. Subsequent research revealed that a number of regularly used household items, including diaper creams, cosmetic colors, disinfectants. It can also result in skin discoloration. This sort

of spot, known as chemical Vitiligo is described as acquired decolouration in genetically sensitive individuals that arises from repeated showing to a specific chemical agent. This type of spot is comparable to idiopathic vitiligo(Mahajan et al., 2024)
Chemical vitiligo is mostly caused by the following mechanisms (Thappa et al., 2012)
(1) Tyrosine, an amino acid that is essential to the formation of melanin, shares a phenolic group with the majority of the toxic compounds in this category. Depigmenting agents seem to interfere with tyrosinase (TYR) to disturb the synthesis of melanin, which results in the formation of depigmented patches.
(2) By triggering the inflammatory cascade in dendritic cells, depigmenting agents may indirectly causemelanocyte (MC) death.
(3) Stress brought on by chemicals triggers autophagy, which in turn causes the synthesis of exosomes and triggers an immunological reaction that ultimately results in the destruction of MC.
Chemical vitiligo has been linked to the following substances: hydrogen peroxide (H2O2), P-phenylenediamine (PPD), and monobenzone (MBZ). In order to improve the patient's overall appearance and eliminate any remaining normal skin tone, these compounds have been utilized to treat patients with severe widespread vitiligo

MBenzone (monobenzone)
Oliver et al. discovered in 1939 that certain tannery workers had discolored patches on their gloved hands, forearms, and on exposed body parts that were not gloved.(Kaushik et al., 2020) To find out more about whether MBZ can cause mice's unexposed skin areas to become less pigmented.(Zhu et al., 2013b) Male C57BL/6 mice that were 4 weeks old were used, and MBZ cream was applied topically to them. They discovered that little white spots gradually became larger after initially emerging in the drug's contact region. These are the creams that cause vitiligo because they contain 20–40% monobenzone. Certain mice also experienced depigmented patches on untreated parts including their tail, ears, and/or trunk following extended MBZ therapy. The depigmented patches became larger over time, finally resulting in the majority of the body becoming depigmented. Higher MBZ concentrations lead to an rise in the percentage of Mice that experienced remote depigmentation as well as the severity of the condition. Ultimately, depigmentation occurred in exposed and some unexposed areas in all MBZ-treated mice. High MBZ concentrations can hasten the onset of vitiligo, but they also cause notable localized irritation and exudation. They came to the conclusion that the best concentration of MBZ cream was 40%. Depigmented skin examined histologically and using Reflectance Confocal Microscopy (RCM) revealed increased infiltration of skin mononuclear cells around distant depigmented lesions, along with the decrease of epidermal MCs and collection of CD8+T lymphocytes surrounding the lesions. While few CD8+ T cells were seen in healthy skin, immunofluorescence labeling using an anti-CD8 antibody demonstrated that a sizable amount of CD8+ T cells were present in the infiltrating lymphocytes. (Arowojolu et al., 2017)These findings imply a connection between the immunological response of T cells and the growth of distal leukoplakia in mice.
Hydrogen Peroxide [H_2O_2]
H2O2 is a powerful oxidizing 2 electron reduction result that is used as among the starting substance to create Hydroxyl-radical. H2O2 can penetrate the cellular layer or harm MC directlly. Additionally, H_2O_2 might influence the synthesis of melanin by the epidermis' oxidation of tetrahydrobiopterin [BH-4] and suppressing the actions of tyrosine hydroxylase (TH), dopaoxidase (DO), and tyrosinase. Following HO exposure, MCs exhibited elevated level of Baxs and cleaved caspase-3 and reduce levels of Bcl-2. The oxidant-antioxidant system's equilibrium can be upset by a variety of endogenous or exogenous stressors, which is able to raise the concentration of Reactive Oxygen Species [ROS] in MC. Nucleic acids, lipids, and proteins are among the macromolecular materials that ROS can degrade. This results in DNA breakage, Oxidative Stress, or lipid peroxidation protein degradation, Moreover, the various enzymes'activation or in-activation.(An et al., 2021)

Furthermore, reactive Oxidative Stress can lead to alterations with in the lipid content a reduce in the Mitochondrial Membrane the effective of the mitochondrial membrane, or a breakdown the Respiratory chain. These circumstances increase MCs' susceptibility to apoptotic stimuli and damage. Elevated hydrogen peroxide levels can exacerbate CXCL10 expression, which can lead to CD8+ T Cell intrusion and subsequent decolouration in halo nevus and vitiligo. A 3% hydrogen peroxide solution is used to treat small cuts and wounds that are healing. Furthermore, oxidative stress triggers the 'unfold protein response' [UPR] or tampers with these 'endo-plasmic reticulum' folding mechanism. The cells die if the MC's adaptive mechanisms are unable to correct the protein folding error. Oxidative damage causes a E-cadherin is downregulated in the cell membrane, which impairs MC adherence to the basement membrane and causes MC apoptosis.(Xuan et al., 2022) In one investigation, black guinea pigs' dorsal skin was depilated to a size of around 40 cm2, and 0.5 ml of a 5% H2O2 For fifty days, the solution was applied twice a day.(Sun et al., 2021) Guinea pigs' black skin turned white throughout that period, and they even developed white hair. A local histological analysis revealed a reduction in melanin concentration in the hair follicles (HF) and spinous layer. There were certain HFs that had black at the bottom, yellow in the middle, and white at the top. There was a concurrent rise in serum concentrations of immunoglobulin (Ig) and monoamine oxidase (MAO), and a fall in cholinesterase (ChE). However, utilizing H2O2 to cause vitiligo in mice has not been successful in multiple trials. They hypothesized that by bleaching the melanin already present, H2O2 causes depigmentation. More newly produced melanin granules may counteract the effect of H2O2 on MC. Although easily managed, H2O2-induced depigmentation does not fully align with the pathophysiology of clinical vitiligo.
Hydroquinone {HQ}
HQ is a common skin-lightening product that functions by blocking TYR's catalyzed conversion of tyrosine to melanin.(Hu et al., 2009) It is unknown how HQ poisoning affects melanocytes (MC). HQ can quickly and spontaneously oxidize in the extra-cellular domain to produce the equivalent O-Quinones and copious amounts of Reactive Oxygen Species (ROS).(Huo et al., 2014)
(2) The para-position of phenol has hydrophobic electron-donating substituents that give it strong cellular penetrable and increase susceptibility to auto-oxidation. Skin depigmentation results after using high concentrations of HQ. Research has demonstrated that a therapeutic use of 2% of HQ cream can successfully lower melanin synthesis by 63.6%. C57BL/6 mice's dorsal skin sections that had been shaved (2 x 2 cm) received a topical treatment of 2 ml of 2.5% HQ every day for 60 days. Hair and white patches eventually developed on the treated sites. Histological examination revealed that, in compare to the control group, the concentration of melanin in HF Mcs, basal MCs, and epidermal Mcs decreased following HQ therapy.

Chickens from Smyth-Line [SL]

The sole animal vitiligo model that naturally displays every both clinical and biochemical symptom associated with human vitiligo is Smyth Line (SL) chickens. The combination of immunological, environmental, and hereditary variables results in SL vitiligo. Susceptibility to SL vitiligo is partially characterized by an intrinsic MC deficiency. Anomalies in humoral immunity and cell-mediated immune responses specific to MC are the causes of MC loss. Human vitiligo is identical to the phenotypic and etiology of SL vitiligo.(Sreekumar et al., 2001) On the other hand, pigmentation loss in SL hens results from pigmented HF and MK feather loss rather than epidermal pigmentation loss.(ERF et al., 2001) SL chickens are therefore unsuitable for research on human vitiligo.

Vitiligo models in mice

Research has demonstrated that T cells, particularly deadly CD8+ T lymphocytes that penetrate the vitiligo lesion margins, facilitate the removal of Mcs or essential, sufficient for the onset progression of vitiligo. Skin resident memory T-cells (TRMs) cause vitiligo relapse, but regulate the T-cells preserve immunological equilibrium or reduce the swelling.(Erf et al., 2020) This notion has led to the development of many vitiligo mouse models.

Mice that are transgenic:

The recipient mice are transgenic mice (KRT14-kitl*4XTG2Bjl, also known as SCF mice), whose epidermis and hair are black, and who express Kit ligand-induced stem cell factor (SCF). To reduce the amount of natural lymphocytes in these mice, gamma radiation at a sublethal dose (5 Gy) was administered. To produce PMEL mice, or GFP-PMEL TCR trans-genic mice, which functioned as donating CD8+ T-cells, 'DPEGEP' mice, that have olive green fluorescent proteid expressed, were mated with T-cellular receptor [TCR] trans-genic mice, expressed pre-melanosome proteid [PMEL]. A weaker version of the 'recombinant vaccinia virus' [rVV] was given I.P then stimulate CD8+ T-cells and cause them to detroy recipient mouse Mcs after CD8+ T cells were intraorbitally injected into SCF animals.(Wang et al., 2021) Depigmented skin appeared on the ears, nose, palms, feet, and tail of SCF mice five to seven weeks later. No more depigmented patches emerged after seven weeks.(Riding et al., 2019) This transgenic mouse models is very helpful for the studying process of repigmentation and these effectiveness of novel treatments for vitiligo because it mimics the course of human vitiligo and maintains the critical function of HF in repigmentation.

C57BL/6 mice:

Research teams have created rVVs expressing several MC-specific antigens in response to the occurrence that Mcs are eliminated by the Immunological cells in the body while treating malignant melanoma (MM).(Scatozza et al., 2020)Eighty percent of ' C57BL/6 mice' injected with rVV expressing people TRP1 developed depigmented skin patches resembling vitiligo, a condition commonly observed in people MM patient receiving IL~12 treatment.(Steitz & Tüting, 2013) The development of these model is brought about by the generation of certain antibodies that cause MC damage as well as the activating of CD4+ T-cell-'Mediated cell immunology'. The immunological mechanisms behind vitiligo can be investigated using this mouse model.

Hybrid mice:

A TYR369-specific transgenic mouse model (called FH mice) was created by crossing 'TYR-partial albino mice with AAD plus mice' that express major Histo-compatibility complex type I [Mhc], the people HLA-A021 binding region, and the TYR 369 pheno-type. (Gregg et al., 2010)After crossing FH mice with AAD+ mice, the progeny exhibited depigmentation of the skin and hair. This model resembles human vitiligo in that it is an autoimmune vitiligo dependent on CD8+ T-cells. In these model, lesions both sides of the head and face in juvenile animals and exclusively on the trunk in older animals were the gradual appearance of depigmented patches. According to this hypothesis, the mechanisms underlying the depigmentation process may vary depending on the body part. With regard to cytokines, immunological pathways, and regional mechanisms, these model maybe utilized then further define the vitiligo of the Immune mechanism.

Vitiligo linked to medication

Whitish halos surrounding these main tumor , regions of white comined with melanoma and non-pigmented spots in scars from melanoma or immunotherapy injection site are some of these characteristics of melanoma-associated depigmented patches. (Daneshpazhooh et al., 2006) Spots that resemble vitiligo that are far from the main tumor are the rarest signs. Numerous studies demonstrate that immunotherapy raises the risk of vitiligo in relation to melanoma. Due to the immunogenic antigens that MM cells and MCs share, such as 'TYRP-1/GP75, TYRP-2, TYR, and GP100' depigmentation may result from the autoimmune-mediated elimination of MM cells as well as normal MCs.(Teulings et al., 2014) According to numerous studies, Compared to the general population, M M patients experience spontaneous vitiligo more frequently. Furthermore, two to sixteen percentage of M M patients causes decolouration macules following cure with immune-suppressants such as Interferon α [IFN-alpha], Interlucine-2, and immunological check-point inhibiting [Anti~cytotoxic T~lymphocyte Antigen-4 or programme cell die inhibitor]. This state is known as Mm linked with Vitiligo, and it share pathophysiological characteristics with Vitiligo. Better immune response, which translates into higher survival than anticipated by melanoma stage, may be predicted by the MAV phenomenon.(Farinazzo et al., 2021) Moreover, the administration of Cyclin-dependent kinase 4 or 6 inhibitor was linked and causes of vitiligo-like decolouration in breast cancer people.(Sollena et al., 2021)

Conclusion

This vitiligo model can be use to induce vitiligo in the animals and test the new drug on how to act in vitiligo. In chemical models like monobenzone cream is easily applied on the rat because it is very simple and easiest model for vitiligo. In chemical models when we induce vitiligo in animals chemical concentration is very important parameter to induce depigmentation in the animals when be not in good concentration it does not cause depigmentation skin. Each animal model has pros and cons of its own, and they can only partially mimic the pathophysiology of human vitiligo. Various models should be selected by researchers based on their particular research interests and objectives when conducting experiments.

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