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Microorganisms in pathogenesis and management of Vitiligo

Prashant Giri[a], Ankit Bharti[b], E. Helen Kemp[c], Mitesh Kumar Dwivedi[a]*

[a]C. G. Bhakta Institute of Biotechnology, Faculty of Science, UkaTarsadia University, Tarsadi-394350, Bardoli, District Surat, Gujarat, India

[b]Aura skin care, Laxmi Icon 2nd Floor, Unai Road, near Swaminarayan Temple, Vyara-394650, Gujarat, India

[c]Department of Oncology and Metabolism, University of Sheffield, Sheffield, S10 2RX, United Kingdom

***Correspondence:** Dr. Mitesh Kumar Dwivedi, C. G. Bhakta Institute of Biotechnology, Faculty of Science, UkaTarsadia University, Bardoli, Surat- 394350, Gujarat, India.

Email: mitesh_dwivedi@yahoo.com

ORCID: 0000-0001-8497-0765

Abstract

Vitiligo is an autoimmune skin depigmentation diseasecharacterized by $CD8^+$ T cells mediated loss of function melanocytes. The role of autoimmunity in the pathogenesis of vitiligo has been well established. However, the exact triggering factors involved in vitiligo development are unclear. The healthy skin microbiome comprises of diverse microbes, including bacteria, archaea, fungi, and viruses; the microbes interact with the immune system and regulate dermatological health. However, recent evidence has suggested the involvement of microbial infections and dysbiosis in the skin microbiome with vitiligo pathogenesis. The changes in the human skin microbiome can play a major role in triggering immune response through various mechanisms such as molecular mimicry, bystander activation, cross-reactivity, epitope spreading, and production of superantigens. Moreover, maintaining the skin microbiome and probiotics-based treatment could lead to novel immune-therapeutics for vitiligo. Given the crucial role of microorganisms in vitiligo development, our chapter focuses on the role of microorganisms in vitiligo pathogenesis. Additionally, we will discuss the therapeutic potential of microorganisms in the treatment of vitiligo.

Keywords: Vitiligo, Skin microbiome, Autoimmunity, Pathogenesis, Treatment, Probiotics

Contents

1. Introduction

Vitiligo is a skin depigmenting disease caused by autoimmune loss of functional melanocytes from the epidermal layer (Nordlund 2011). The prevalence of vitiligo ranges from 0.5 to 2% worldwide (Bergqvist and Ezzedine 2020).Vitiligo might be considered a minor disease but has serious implications as patients suffer from a lot of mental stress, embarrassment, social stigma, which affects them psychologically as it results in low self-esteem in social situations(Grimes and Miller 2018). Despite enormous research in the field, the exact etiology of vitiligo is obscure (Mohammed et al. 2015). Studies suggest that factors like genetics, physical trauma, stress, emotional imbalance, environment, oxidative stress and autoimmunity could trigger vitiligo development (Colucci et al. 2015; Manga et al. 2016; Henning et al. 2020). After the initial trigger, the autoimmune aspect of vitiligo pathogenesis has been well documented as studies suggest cytotoxic T cells mediated loss of functional melanocytes in vitiligo patients (Wu et al. 2013). Moreover, the importance of autoimmunity, oxidative stress and genetics has been backed by previous studies. These suggest the involvement of immune system-associated genes such as *forkhead boxp3 (FOXP3), interferon-gamma (IFNG), interleukin 4 (IL4), proteasome 20S subunit beta 8 (PSMB8), NLR family pyrin domain containing 1 (NLRP1), neuropeptide Y (NPY),* and *interleukin-1-beta (IL1B)*, as well as increased LPO (abbrev) levels in vitiligo patients (Imran et al. 2012; Laddha et al. 2013a; Dwivedi et al. 2013c; d; Laddha et al. 2014b; Jadeja et al. 2017; Giri et al. 2021). However, despite the recent advancement, there is no definitive treatment option available for vitiligo and remission is common for the currently available therapies.

The role of microorganisms in autoimmune diseases is gaining traction as studies suggest that the human microbiome can be a major player in triggering autoimmunity (De Luca and Shoenfeld 2019). The changes in the microbial composition could lead to prolonged infection, bystander activation and molecular mimicry, triggering loss of immune tolerance against the host itself (Arango et al. 2013). Moreover, dysbiosis and reduction in the complexity of the human microbiota lead to an altered immune response in autoimmune diseases (Zheng et al. 2020), as alterations in the gut microbiota have been shown to be associated with various autoimmune disease like rheumatoid arthritis (RA), type 1 diabetes (T1D), systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD) and multiple sclerosis (MS) (De Luca and Shoenfeld 2019).

Interestingly, a reduced cutaneous microbial diversity has been observed in vitiligo patients (Ganju et al. 2016). However, the exact role of microbiota in vitiligo pathogenesis and

progression is unclear as detailed studies on the microbial diversity in vitiligous skin are lacking. Therefore, the current chapter focuses on the role of microorganisms in vitiligo pathogenesis and the management of vitiligo.

2. The role of autoimmunity in vitiligo pathogenesis

Vitiligo is a complex skin depigmenting disease. Several factors including infections, genetics, stress, altered melanocyte adhesion, oxidative stress, and autoimmunity, are considered to play a part in vitiligo pathogenesis (Dwivedi et al. 2015; Rashighi and Harris 2017). Indeed, many studies suggest a role of the innate and adaptive immune responses in vitiligo pathogenesis (Laddha et al. 2013b; Richmond et al. 2013, 2019). Moreover, evidence suggests the breakdown of free radical defence may be responsible for melanocyte destruction (Jadeja et al. 2021). Here, we will discuss the role of autoimmunity and oxidative stress in vitiligo pathogenesis.

2.1. Oxidative stress mediated autoimmunity

Oxidative stress is considered as one possible theory for vitiligo aetiology. Reactive oxygen species (ROS), such as hydrogen peroxidase and peroxynitrate, have been observed in the skin of vitiligo patients (Laddha et al. 2013a; Colucci et al. 2015). Moreover, melanocytes are highly susceptible to oxidative stress as melanin production requires high energy consumption (Denat et al. 2014). In addition, the high levels of ROS generated during melanogenesis, and the low levels of antioxidant enzymes such as catalase, glutathione peroxidase, glucose 6-phosphate dehydrogenase and superoxide dismutase lead to high levels of ROS in the melanocytes of vitiligo patients (Agrawal et al. 2004; Laddha et al. 2013b). The increased ROS species accumulation leads to DNA damage, increased pro-inflammatory and anti-melanogenic cytokines production, lipid peroxidation and the loss of functionality of melanogenesis-related enzymes (Jadeja et al. 2021; Chen et al. 2021).

Oxidative stress during melanogenesis results in the accumulation of misfolded proteins in the endoplasmic reticulum (ER) (Jadeja et al. 2021). Additionally, previous studies have suggested ER stress can lead to breakdown of immune tolerance by activating the unfolded protein response (UPR) (Manga et al. 2010; Jadeja et al. 2021). Several ER-related chaperons like HSP70i serve as damage-associated molecular patterns (DAMPs) to innate immune cells when they are translocated to the cell surface or released in the extracellular space (Richmond et al.

2013). This leads to phagocytosis and antigen presentation of melanocyte-specific antigens by innate immune cells, which subsequently activate the adaptive immune response against melanocytes (Richmond et al. 2013). Additionally, increased oxidative stress in melanocytes leads to translocation of calreticulin to the melanocyte cell surface (Zhang et al. 2014), which further increases melanocyte immunogenicity.

2.2. The role of the innate immune response in vitiligo pathogenesis

The innate immune system is the first line of defence against pathogens. The pathogen-associated molecular patterns (PAMPs), DAMPs, toll-like receptors (TLRs) and pattern recognition receptors (PRRs) are essential in the activation of the immune response. Several DAMPs have been recognized in vitiligo patients (Richmond et al. 2013). Additionally, genome-wide association studies (GWAS) have identified the role of PRRs, particularly TLRs, in vitiligo susceptibility (Richmond et al. 2013). Viral infections are generally known to activate immune response as viruses possess PAMPs like RNA, DNA, and glycoproteins which could initiate the innate immune response in vitiligo (Mogensen 2009). Additionally, bacterial infections, the major PAMP producers, could direct an immune response against self-antigens in vitiligo (Mogensen 2009). Although the direct role of viruses and microbes in vitiligo pathogenesis is unknown, dysbiosis in the skin microbiome in lesional skin is linked to vitiligo pathogenesis (Ganju et al. 2016).

NLRP1 is a critical regulator of the innate immune response; it recognizes PAMPs triggering NLRP1 inflammasome formation, which activates the apoptotic and inflammatory pathways resulting in vitiligo pathogenesis (Dwivedi et al. 2013c). Additionally, previous genetic association studies have suggested the association of NLRP1 with vitiligo susceptibility (Dwivedi et al. 2013c). Moreover, overexpression of NLRP1 in immune cells of vitiligo patients could initiate melanocytes apoptosis (Dwivedi et al. 2013c). Previous studies have highlighted the role of neuropeptide-Y (NPY) in triggering the inflammatory immune response in vitiligo patients, as *NPY* exon 2 +1128 T/C, 2399 T/C and *IL1B* 2511 C/T polymorphisms correlated with increased IL-1β levels leading to autoimmunity (Laddha et al. 2014b). The genetic association polymorphisms in the *PSMB8* gene in vitiligo patients suggest altered antigen processing could lead to T cell-mediated melanocyte destruction (Jadeja et al. 2017).

Earlier studies have shown infiltration of the critical innate immune cells like macrophages, Langerhans cells, dendritic cells (DCs), natural killer (NK) cells in the lesional skin of vitiligo

patients (Boniface et al. 2021). Moreover, Fc-γ receptor-expression on melanocytes and macrophage migration inhibitory factors which activate macrophages play an important role in autoimmunity in vitiligo (Farag et al. 2018). Additionally, the presence of CD11c+ dermal dendritic cells, CD207+ Langerhans cells and expression of TRAIL on dendritic cells leads to melanocytes apoptosis (Kroll et al. 2005). Interestingly recent studies have suggested increased NK cells and innate lymphoid cells (ILC1) in vitiligo patients (Tulic et al. 2019). Gene expression studies have revealed overexpression of β-defensin and CLEC2B, responsible for NK cells activation, in vitiligo patients (Yu et al. 2012). Key activation markers of NK cells like NKG2D have also been found at increased levels in those with vitiligo (Grau et al. 2018). The increased infiltration of innate immune cells in vitiligo patients leads to overproduction of key inflammatory cytokines like IL-2, IL-4, IL-6, IFN-γ, TNF-α, TNF-β and IL-1β (Gholijani et al. 2020). These cytokines activate the adaptive immune response against melanocytes. In addition, melanocytes are surrounded by keratinocytes which are capable of producing TNF-α (Laddha et al. 2012b), which leads to increased inflammation and immune responses through activation of NF-κB (Liu et al. 2017). TNF-α binds to TNFR1 and TNFR2 receptors expressed by melanocytes under stress leading to caspase-mediated melanocyte death (Camara-Lemarroy and Salas-Alanis 2013; Webb et al. 2015). TNF-α also binds to TNF-related apoptosis-inducing ligand (TRAIL) inducing apoptosis in melanocytes (Camara-Lemarroy and Salas-Alanis 2013). Furthermore, it also inhibits melanocyte proliferation by upregulating CXC-chemokine receptor II expression (Lee et al. 2013) (Lee et al., 2013). The cytokine can also inhibit melanogenesis by suppressing the expression of tyrosinase and tyrosinase-related protein 1 (Englaro et al. 1999; Singh et al. 2021). TNF-α and IFN-γ can increase T cell-mediated cytotoxicity of melanocytes by increasing adhesion molecules like intercellular adhesion molecule-1 (ICAM-1) (Laddha et al. 2012b; Singh et al. 2021). Interestingly, ICAM-1, TNF-α and IFN-γ expression is increased in vitiligo patients (Laddha et al. 2012b).

Overall, the previous evidence suggests that the DAMPs act as ligands for PRR, which results in the activation of innate immune response in vitiligo patients. The activated innate immune response leads to overproduction of inflammatory cytokines and eventually leads to activation of the adaptive immune response resulting in melanocytes destruction.

2.3. The role of the adaptive immune response in vitiligo pathogenesis

The role of the adaptive immune response has been well established in vitiligo as studies suggest cytotoxic T cells mediated destruction of melanocytes in vitiligo patients (Laddha et

al. 2014a; Dwivedi et al. 2015). The presence of melanocyte-specific $CD8^+$, $CD4^+$, $CD8^+$ TRM cells and melanocytes specific autoantibodies further confirms the crucial role of the adaptive immune response in vitiligo pathogenesis (Waterman et al. 2002; Lambe et al. 2006; You et al. 2013; Shah et al. 2021).

The role of T cells in vitiligo pathogenesis has been widely studied (Dwivedi et al. 2015; Giri et al. 2020b). Studies have found infiltration of CD8+ and CD4+ T cells in the skin of vitiligo patients (Waterman et al. 2002; Lambe et al. 2006; You et al. 2013; Shah et al. 2021). Additionally, the infiltrated T cells are melanocyte-specific as they recognize the key melanocytes antigens MART-1, PMEL and tyrosinase (Hoashi et al. 2005; Le Poole and Luiten 2008). Furthermore, they express skin homing markers (Ogg et al. 1998). The T cells present in the skin of vitiligo patients are activated, and the overexpression of granzyme B and perforin by these cytotoxic T cells suggests that there is T cell-mediated destruction of melanocytes in vitiligo patients (Riding and Harris 2019). An interesting recent study indicates that $CD8^+$ T cells recognize melanocytes via natural killer group 2D (NKG2D), an activating receptor expressed by killer lymphocytes (Plaza-Rojas and Guevara-Patiño 2021). Under stress, melanocytes express NKG2DL leading to CD8+ T cells killing (Plaza-Rojas and Guevara-Patiño 2021).

Tissue-resident memory T cells (TRM) have been shown to express increased NKG2D levels leading to the overproduction of IFN-γ and TNF-α (Grau et al. 2018). Our recent study has highlighted the role of TRM cells in vitiligo pathogenesis (Shah et al. 2021). $CD8^+$ TRM cells suppress melanocytes, preventing repigmentation and are thought to inhibit regulatory T cells (Tregs) (Frączek et al. 2020). Elevated T helper 17 (Th17) cells have been found in the lesional skin of vitiligo patients (Wang et al. 2011). Moreover, the FAS-FASL-dependent destruction of melanocytes by autoreactive $CD4^+$ T cells highlights the role of $CD4_+$ T cells in vitiligo pathogenesis (Lambe et al. 2006). Th17 cells suppress melanocytes function and activity by downregulating melanin production (Kotobuki et al. 2012), and also induce the production of key inflammatory cytokines IFN-γ, TNF-α, TNF-β and IL-1β by keratinocytes and fibroblasts. This can lead to caspase-mediated apoptosis of melanocytes (Kany et al. 2019).

In contrast to the widely reported T cells-mediated melanocytes destruction, the role of B cells in vitiligo pathogenesis is unclear. However, B cell circulation has been found to be increased in vitiligo patients (Willemsen et al. 2021). Differentiation of antibody-secreting B cells and production of melanocyte-specific autoantibodies by B cells have been shown to be increased

in vitiligo patients (Willemsen et al. 2021). Melanocyte-specific autoantibodies have been linked with disease activity as well (Willemsen et al. 2021). Previous reports have found increased autoantibodies against PMEL17, melanoma antigen recognized by T-cells (MART1), tyrosine hydroxylase (TH), tyrosine-related protein-2 (TRP2), tyrosinase-related protein-1 (TRP1), tyrosinase, melanin-concentrating hormone receptor-1 (MCHR1), melanocortin 1 receptor (MC1R), VIT75, VIT90 VIT40, HSP70, HSP90, Rab38, and translation-initiation factor 2 (Kemp et al. 1998; Palermo et al. 2001; Waterman et al. 2002; Gavalas et al. 2009; Li et al. 2011; Willemsen et al. 2021). These autoantibodies can direct complement-mediated damage and antibody-dependent cellular toxicity (Schmitz et al. 1995). Furthermore, they can increase ICAM-1 mediated melanocyte apoptosis and also increase antigen presentation of melanocytes (Laddha et al. 2012b).

Tregs maintain peripheral tolerance by controlling aberrant autoimmune responses by self-reactive T cells (Giri et al. 2021). However, flow cytometric analyses have found reduced Tregs in vitiligo patients (Dwivedi et al. 2013b). Our previous study has suggested an imbalance in $CD8^+$ T cells and Tregs as the CD8/CD4 T cell ratio was found to be reduced in vitiligo patients (Dwivedi et al. 2013b). Interestingly, the decreased Tregs were more prominent in active vitiligo patients (Tembhre et al. 2013). Apart from defects in Treg frequency, earlier studies have also found decreased Treg suppressive function in vitiligo patients (Giri et al. 2020b). Our recent studies have suggested the reduced NFATs and FOXP3 levels, both key Treg transcription factors, lead to reduced downstream immune regulatory genes, thereby leading to decreased Treg mediated suppression of $CD8^+$ and $CD4^+$ T cells (Giri et al. 2020a; b, 2021). In addition, the role of NFAT signalling pathways as calcium-controlled activation of NFATc1 enhanced Treg suppressive function in vitiligo patients (Dwivedi, unpublished data). Studies have also explored the role of Treg cells in vitiligo treatment as emerging studies have suggested that adoptive Treg transfer prevents progressive depigmentation in the H3TA2 vitiligo mice model and can be employed for vitiligo treatment (Chatterjee et al. 2014; Eby et al. 2014). Recently, antigen-specific (GD3) CAR Tregs have been shown to reduce autoimmune reactions and thereby contribute to decreased depigmentation in vitiligo mouse model (Mukhatayev et al. 2020). A recent study provided new insights in Treg function suggesting that the expression of CCR5 on Tregs is necessary for Treg function and vitiligo control in vivo (Gellatly et al. 2021). We have also proposed the role of probiotics and prebiotics in Treg-mediated therapeutics of generalised vitiligo (Dwivedi et al. 2016).

Overall, the studies suggest multiple triggering factors like infections, genetics, stress, altered melanocyte adhesion, oxidative stress, and autoimmunity can lead to innate immune system activation, which results in a widespread activation of $CD4^+$ T cells, $CD8^+$ T cells and B cells. Moreover, the altered Treg cells number and suppressive function lead to unchecked proliferation of $CD4^+$ T cells and $CD8^+$ T cells, which results in melanocytes destruction leading to vitiligo pathogenesis (Figure 1).

3. Skin microbiota and immune system

The trillions of bacteria living inside the gut are understood to be important for maintaining immune homeostasis(Khan and Wang 2020). However, there is another microbiome called the skin microbiome which is gaining attention recently. The skin microbiome consists of diverse bacteria, archea, fungi, viruses and eucaryotes, which interact with the immune system and regulate dermatological health (Byrd et al. 2018). The skin microbiota, epithelial cells and immune cells communicate with each other to maintain skin homeostasis and eliminate possible pathogens (Byrd et al. 2018).

3.1. Skin microecology

Although the skin is a harsh, dry, nutrient-poor environment, it consists of diverse microbial compositions as the healthy adult skin is found to be abundant with bacteria, fungi, and viruses(Byrd et al. 2018). The microbial community present in the skin helps create an environment that is the first line of defence against microbial pathogens. Microbes such as *Staphylococcus epidermidis* and *Cutibacterium* reside in the skin and communicate with the host cells to produce anti-microbial peptides which protect the host from bacterial infections(Cogen et al. 2008). *Cutibacteria acnes* produce an acidic environment that becomes inhospitable to invading pathogens (Flowers and Grice 2020). Additionally, *S epidermidis* produces chemicals that suppress inflammation and thereby help in producing tight junction between the skin cells, which protect from invading infections (Cogen et al. 2008).

Firmicutes, Proteobacteria, Actinobacteria and *Bacteroidetes* are found to be in most abundance in the skin microenvironment (Grice and Segre 2011). However, the bacteria composition in the skin microenvironment mostly dependents on the physiology of the skin site i.e, the *Propionibacterium* species are dominant in the sebaceous sites (McLaughlin et al.

2019). In contrast, *Staphylococcus* and *Corynebacterium* are present in the moist sites (Byrd et al. 2018). Fungal communities are found throughout the body; however specifically, *Malassezia* is dominant in the moist areas, whereas *Aspergillus, Epicoccum, Cryptococcus* are found in the foot area (Saunders et al. 2012; Byrd et al. 2018). Other than bacteria and fungi, viruses have been found to colonize the skin microbiome, as suggested by the presence of human papillomavirus (Foulongne et al. 2012). DNA viruses have been found to be present on the skin surface (Foulongne et al. 2012). The presence of eukaryotes like Demodex mites in the sebaceous sites suggests the involvement of arthropods in the skin microbiome (Grice and Segre 2011).

Shortly after birth, the commensal bacteria induce Tregs to tolerate commensal microbes (Zheng et al. 2020). The delicate balance in the skin microbiome is essential for maintaining dermatological health, but it can sometimes falter and dysbiosis can lead to dermatological conditions such as acne, atopic dermatitis, psoriasis, and vitiligo (De Pessemier et al. 2021). Some strains of *C. acnes* can produce pro-inflammatory molecules that are associated with sores and acnes (Mayslich et al. 2021). *S. epidermidis* can cause opportunistic infections (Otto 2009). The dysregulated immune response can also cause chronic disorders like vitiligo, psoriasis and atopic dermatitis (AD). The presence of bacterial species like *Firmicutes, Propionibacterium, Actinobacteria, Staphylococcus* can cause acute lesions in the skin (Grice and Segre 2011).

Antimicrobial peptides released by bacterial infection can activate DCs (Diamond et al. 2009). These, in turn, promote T cells differentiation which can be observed by the accumulation of T cells and DCs in psoriatic lesions (Cai et al. 2012). The $CD4^+$ T cells then produce IL-17 and IFN-γ, which stimulates the proliferation of keratinocytes leading to thickening of the epidermis (Cai et al. 2012). Thus, the cross-talk between microbial infection, keratinocytes, and immune cells lead to tissue remodelling and amplification of the dysregulated immune response.

S. aureus has been found to be linked with various skin diseases as it has the ability to modulate the immune response (Otto 2014). The δ-toxin released by *S. aureus* results in mast cell degranulation (Nakamura et al. 2013). *S. aureus* α-toxin also promotes the production of IL-1β by monocytes which leads to activation of the Th17 response (Niebuhr et al. 2011; Bonifacius et al. 2020). In addition, *S. aureus* has been found in the skin of AD patients, suggesting it can lead to epidermal impairment and immune cell-activation resulting in AD (Kim et al. 2019). A

decline in microbiome diversity has been observed in vitiligo (Ganju et al. 2016). Interestingly, recent studies have shown that probiotic treatments can restore the balance of the skin microbiome (Paetzold et al. 2019). Therefore, understanding the complex interactions between the skin microbiome and the immune system may lead to novel therapeutic strategies to combat skin-related diseases.

3.2. Skin immune barrier

The skin is the body's primary barrier against physical insults and microbial pathogens (Nguyen and Soulika 2019). It represents a unique environment in which skin cells interact with immune cells to provide tissue homeostasis and induce immune responses (Nguyen and Soulika 2019). The skin is composed of the epidermis, dermis and a subcutaneous fatty region (Yousef et al. 2021). The epidermis is composed of highly specialized epithelial cells known as keratinocytes (Yousef et al. 2021). They are continuously replenished from the layer of basal keratinocytes, which divide frequently (Yousef et al. 2021). Dead cells called corneocytes are located in the outermost layer and are largely responsible for the barrier function in the skin (Yousef et al. 2021). Melanocytes are located in the basal layer of the epidermis, and they are oval, fusiform DCs (Cichorek et al. 2013). They are identifiable by the expression of tyrosinase, tyrosine-related protein-1 and -2, PMEL17, and MART-1 (Cichorek et al. 2013). They are surrounded by keratinocytes at a ratio of about 1: 10 (Cichorek et al. 2013). In the dermis, cells known as fibroblasts secrete elastin and collagen fibres that form a dense extracellular matrix (Tracy et al. 2016). Blood capillaries irrigate the dermis while lymph fluid is drained thorough lymphatic vessels to lymph nodes, specialized immune system in which immune cells are activated after pathogen encounter (Alberts et al. 2002). Here, diverse and functionally specialized immune cells populate the skin (Alberts et al. 2002).

The commensal bacteria, viruses and fungi living on the skin have beneficial effects in protection against pathogens and wound healing (Byrd et al. 2018). In the epidermis, specialized subsets of DCs called Langerhans cells detect antigens; they project dendrites upwards towards the cornified epithelial cells and sample bacteria antigens like toxins (Romani et al. 2010). Langerhans cells appear to be both anti-inflammatory and activators of immune response depending on their context (Clayton et al. 2017). DCs in the dermis are highly efficient at capturing dead cells and presenting antigens such as viruses, other intracellular pathogens, and skin-associated self-antigens to T cells; thus, DCs are thought to be immune sentinels, whereas the T cells are the immune effector cells (Stockwin et al. 2000).

Healthy skin cells contain twice the number of T cells compared to blood; most of them are memory T cells that have previously encountered antigens(Koguchi-Yoshioka et al. 2021). $CD8^+$ T cells, a subset that becomes cytotoxic and kills target cells upon activation, whereas $CD4^+$ T cells which has a modulatory role in the immune response(Koguchi-Yoshioka et al. 2021). A variety of other cells such as NK cells, mast cells, eosinophils are present in the dermis(Portales-Cervantes et al. 2019). DCs and keratinocytes sense tissue damage such as wound or cold sore lesions through PAMPs or host-derived molecules such as DNA. Keratinocytes produce antimicrobial peptides which kill bacteria directly, inflammatory mediators such as IL-1, which activate DCs and chemokines, which recruit macrophages, neutrophils and T cells (Nestle et al. 2009; Nguyen and Soulika 2019). Activated DCs migrate to the lymph nodes where they present antigen to naïve T cells priming them to activate and differentiate into effector T cells. Effector T cells migrate to the skin, where they kill infected keratinocytes, viral infections and also secrete other cytokines that recruit other immune cells(Charles A Janeway et al. 2001; Nestle et al. 2009; Nguyen and Soulika 2019). Following clearance, Tregs control the immune response, whereas memory T cells persist in the skin to provide protection against subsequent infection with the same pathogen(Charles A Janeway et al. 2001; Nestle et al. 2009; Nguyen and Soulika 2019).

Immune responses can become deregulated and cause skin disorders such as vitiligo, psoriasis, and AD (Campione et al. 2020). Vitiligo is a skin depigmenting disease characterized by white patches due to the autoimmune loss of functional melanocytes (Dwivedi et al. 2013a). Multiple factors such as bacteria or viral infections, genetic makeup, environment, oxidative stress, and physical stress can confer susceptibility to vitiligo (Laddha et al. 2013b). Stressed melanocytes, physical injury, infections can lead to recognition of melanocytes by DCs (Bergqvist and Ezzedine 2020). Together with IL-1, TNF-α and IFN-γ secreted by keratinocytes and DCs, T cells become activated (Wang et al. 2011; Bergqvist and Ezzedine 2020; Giri, P. S., Dwivedi 2021). Activated $CD4^+$ T cells then activate cytotoxic $CD8^+$ T cells; the $CD8^+$ infiltrate the epidermis and perform their cytotoxic function leading to melanocyte death (Frisoli et al. 2020; Katz and Harris 2021). T cells and keratinocytes produce a high amount of TNF-α and IFN-γ cytokines, which increases T cells mediated cytotoxicity towards melanocytes (Laddha et al. 2012a; Dwivedi et al. 2013d). Tregs in vitiligo patients are low in number (Dwivedi et al. 2015; Tembhre et al. 2015). They are also non-functional, leading to an aberrant autoimmune responses (Lili et al. 2012; Giri et al. 2020b). Additionally, T cells reside in the skin lesions and become resident memory T cells (TRM), where they block skin repigmentation by killing

melanocytes (Frączek et al. 2020). Thus, immune cells in the skin exert important barrier functions (Koguchi-Yoshioka et al. 2021). However, dysbiosis in the skin microbiome can lead to a deregulated immune response against self-antigens that could cause autoimmunity (Figure 1) (Murphree 2017; Byrd et al. 2018; Nguyen and Soulika 2019).

4. Role of microorganisms in pathogenesis of vitiligo

Vitiligo is progressive skin depigmenting disease, which is characterized by melanocytes destruction mediated by self-reactive cytotoxic T cells (Bergqvist and Ezzedine 2020). Although the triggering factors for vitiligo development are unclear, multiple factors such as genetics, oxidative stress, emotional and hormonal imbalance, infections may be involved in vitiligo development (Bergqvist and Ezzedine 2020). The role of cutaneous bacteria in the development of skin diseases has been suggested, as *Propionibacterium acnes* causes acne, and *S. aureus* leads to psoriasis and AD development (Francuzik et al. 2018; Chang et al. 2018). Although microbial diversity helps in maintaining immune homeostasis, a breach in skin integrity can lead to various skin-related disorders (Murphree 2017). Interestingly, the depigmented skin lesions of vitiligo patients have been shown to have reduced microbial diversity, suggesting the crucial role of microorganisms in vitiligo pathogenesis (Ganju et al. 2016; Bzioueche et al. 2020).

4.1. Potential mechanisms by which infections trigger autoimmune vitiligo

The role of microorganisms in the development of autoimmunity has been evident as previous studies have shown the participation of infections in triggering autoimmunity (Arango et al. 2013). Vitiligo is a multifactorial disease as environmental factors; epigenetics, genetics and stress can lead to vitiligo development (Dwivedi et al. 2015; Bergqvist and Ezzedine 2020). However, not all individuals who are exposed to all the factors develop vitiligo, which suggests that other factors such as the skin microbiome may synergistically act with other factors leading to vitiligo development (Ganju et al. 2016; Bzioueche et al. 2020). Therefore, a dysbiosis in the skin microbiome may lead to skin depigmentation.

4.1.1. **Molecular mimicry:** There are multiple factors through which microorganisms can trigger autoimmune vitiligo, one of which is molecular mimicry (Arango et al. 2013). The term molecular mimicry suggests that infections agents can present antigens similar to host self-antigens(Arango et al. 2013). Thus, molecular mimicry

can lead to cross-reaction, which can activate self-reactive T and B cells resulting in an autoimmune response(Arango et al. 2013). Experimental evidence suggests microorganism's *Helicobacter pylori*, *Campylobacter jejuni*, and viruses such as Herpes simplex virus, Epstein bar virus and cytomegalovirus can trigger various autoimmune diseases through molecular mimicry (Moran and Prendergast 2001; Smatti et al. 2019). Previous studies have suggested the role of *Helicobacter pylori*, Epstein bar virus, cytomegalovirus in the development of vitiligo (Doğan et al. 2014; Dwivedi et al. 2018). Although molecular mimicry is a potential mechanism by which microorganisms can trigger the development of autoimmunity, it alone is not sufficient to develop autoimmunity.

4.1.2. **Bystander activation:** The other crucial mechanism is bystander activation (Arango et al. 2013). The inflammatory response against pathogens can lead to the activation of T and B cells with different specificity (Arango et al. 2013). The non-antigenic activation can lead to an autoimmune response (Pacheco et al. 2019). The activation is triggered by different pathways such as inflammatory response, cytokines, chemokines and PAMPs. Viruses such as Epstein bar virus, cytomegalovirus, and influenza, and bacteria such as *Legionella pneumophila, Listeria monocytogenes,* and microbial lipopolysaccharides have been demonstrated to trigger bystander activation of self-reactive T cells, B cells, NK cells and DCs in autoimmune diseases (Fujinami et al. 2006; Arango et al. 2013; Jung et al. 2017; Dwivedi et al. 2018; Pacheco et al. 2019). Epstein bar virus, cytomegalovirus, influenza, *Chlamydia trachomatis* and microbial lipopolysaccharides have been associated with vitiligo development (Dwivedi et al. 2018) suggesting bystander activation may be involved in its development.

4.1.3. **Epitope spreading:** The third mechanism is epitope spreading, in which autoimmune response is generated through spatial proximity and similarities between microbial epitopes and self-epitopes (Arango et al. 2013). The importance of epitope spreading is evident by the *Mycobacterium leprae* infection. The *M. leprae*, the causative agent for leprosy, has a predilection for peripheral nerves such as Schwann cells (Dupin et al. 2003; Oyarbide-Valencia et al. 2006), which are closely related to melanocytes (Dupin et al. 2003; Oyarbide-Valencia et al. 2006). Therefore, *M. leprae* infection can cause cross-reactivity or epitope spreading against melanocytes (Dupin et al. 2003; Oyarbide-Valencia et al. 2006) and suggests the importance of cross-reactivity and epitope spreading as an important

triggering factor for autoimmune vitiligo development (Dupin et al. 2003; Oyarbide-Valencia et al. 2006). Moreover, it also explains the similarities between lesions of leprosy and autoimmune vitiligo.

4.1.4. **Superantigens:** Bacterial and viral proteins can develop superantigens which can activate multiple T cells, and B cells, which are similar to epitope spreading, can lead to activation of self-reactive T and B cells resulting in autoimmune vitiligo (Acha-Orbea 1993). The persistence of infections like hepatitis C virus, hepatitis B virus, and HIV in vitiligo patients may trigger autoimmunity as a result of constant activation of the immune response (Dwivedi et al. 2018). Therefore, microbial infection through various mechanisms such as molecular mimicry, bystander activation, epitope spreading, superantigens, and constant aviation of immune response can trigger autoimmune vitiligo (Figure 1).

4.2. Dysbiosis of microbial community in lesional and non-lesional vitiligo skins.

Vitiligo is considered an autoimmune skin disease. However, the role of microorganisms has been recently explored in the triggering of the autoimmune response in vitiligo (Ganju et al. 2016; Bzioueche et al. 2020). Although it would be naïve to suggest that the skin microbiome is the sole cause of autoimmune vitiligo as there are multiple factors that can trigger vitiligo development(Bergqvist and Ezzedine 2020). Healthy skin consists of a wide range of microbes forming the skin microbiome, which is crucial for maintaining the immune homeostasis in the skin (Grice and Segre 2011; Byrd et al. 2018). The importance of the skin microbiome has been established as dysbiosis in the skin microbiome associated with various skin-related disorders, including vitiligo (Ganju et al. 2016; Murphree 2017; Byrd et al. 2018; Nguyen and Soulika 2019; Bzioueche et al. 2020). Apart from this, dysbiosis in the gut microbiome can also lead to variation in the skin microbiome leading to vitiligo pathogenesis(Ganju et al. 2016; Bzioueche et al. 2020). Overall, the studies emphasize the importance of skin microbiome in vitiligo pathogenesis (Table 1).

4.2.1. Bacteria

The current understanding suggests a complex interplay between environment, genetics, epigenetics, infections and stress triggers the development of autoimmune vitiligo (Laddha et

al. 2013b; Bergqvist and Ezzedine 2020). A previous study indicated a decrease in the microbial diversity in the lesional skin was associated with vitiligo development (Ganju et al. 2016). The study found that bacterial genera like *Methylobacterium* were exclusive to the lesional skin (Ganju et al. 2016), whereas *Anaerococcus, Microbacterium, Streptophyta* and *Nocardiodes* were found only in the non-lessional skin (Ganju et al. 2016). The metagenomics study suggested that the operation taxonomic units (OTUs) belonging to *Enhydrobacter, Paracoccus, Streptococcus* and *Staphylococcus* were only found in the lesional skin (Ganju et al. 2016). Additionally, the OTUs belonging to *Janibacter* and *Brevundimonas* were exclusive to the non-lesional skin samples (Ganju et al. 2016). Approximately 39 taxa were found to be different between the lesional and non-lesional skin; specifically, *Skermanella, Novosphingobium, Roseomonas, Cellvibrio, Turicibacter, Erysipelotrichaceae* and *Erysipelotrichales* (Ganju et al. 2016). Taxa belonging to *Actinobacteria* and *Proteobacterial* lineage were more abundant in non-lesional skin whereas, *Firmicutes* were predominant in the lesional skin (Ganju et al. 2016). Overall, the decrease in microbial diversity in the lesional skin could hamper the protective skin barrier, aggravating the disease (Figure 1).

Ganju and colleagues have extensively studied microbial diversity; however, the mechanism leading to vitiligo development was not explored (Ganju et al. 2016). The possible mechanisms may be explained as in psoriasis, a disease similar to vitiligo. In the case of psoriasis, the *Streptococcus* and *Staphylococcus* bacteria generate superantigens that could activate a wide variety of T cells, including melanocyte-specific self-reactive T cells (Atefi et al. 2014). Furthermore, the antigens produced by the bacteria through molecular mimicry enhance DC- and keratinocyte-mediated inflammation (Lowes et al. 2014). The superantigens increase T helper cell-mediated IFN-γ production (Leung et al. 1995; Lowes et al. 2014). In vitiligo, it has been observed that there is increased IFN-γ resulting in increased adhesion molecule ICAM-1 expression on melanocytes which subsequently increases T cell-mediated melanocyte cytotoxicity (Dwivedi et al. 2013d). IFN-γ also inhibits melanogenesis in vitiligo (Cai et al. 2019). Therefore, as reported in psoriasis the increased inflammation, T cells activation and IFN-γ production by bacterial species can lead to melanocyte destruction.

Interestingly a previous study suggested that antibiotic treatment alters skin and gut microbiome resulting in vitiligo development (Dellacecca et al. 2020). Specifically, the antibiotic treatment resulted in a marked decrease in *Alkaliphilus, Dysgonomonas,*

Odoribacter, Oscillospira, Pedobacter, Parabacteroides and *Ruminococus* (Dellacecca et al. 2020) in contrast to *Pseudomonas aeruginosa* and *Bacteroides vulgatus* that resided in the skin after antibiotic treatment (Dellacecca et al. 2020). The study found that the reduced microbial diversity resulted in increased B cell and T cell activity resulting in melanocyte destruction (Dellacecca et al. 2020).

Other studies have suggested a decrease in *Cutibacterium, Proteobacterium, Gammabacterium, Acintobacter* and *Paracocus* in vitiligo lessional skin (Bzioueche et al. 2020). Apart from the skin microbiome, the above study also suggested dysbiosis of the gut microbiota as gut microbial α-diversity lowered in vitiligo patients, whereas the firmicutes and *Bacteroidetes* fraction increased in the gut (Ni et al. 2020). *Bifidobacterium* was depleted in lesional skin whereas *Enterococcus, Mycoplasma, Veillonella, Intestinibacter, Bacteroides, Escherichia-Shigella, Parabacteroides, Bifidobacterium,* and *Streptococcus* were found to be increased in non-lesional skin (Bzioueche et al. 2020). The study carried out an in-depth analysis to investigate the correlation between the altered skin microbiome and immune response (Bzioueche et al. 2020). It found that the microbiome changes in the skin activated the innate immune response, as the DAMPs or PAMPs generated by the microbial species led to increased secretion of pro-inflammatory cytokines such as IFN-γ, and chemokines such as CXCL9, CXCL10 and CXCL16 (Bzioueche et al. 2020). These cytokines then led to activation and trafficking of CD8+ T cells to the vitiligo lesions (Bzioueche et al. 2020). IFN-γ also inhibits melanogenesis and increases ICAM-1 expression on melanocytes, resulting in CD8+ T cell-mediated destruction of melanocytes (Figure 1)(Table 1) (Dwivedi et al. 2013d).

4.2.2. Viruses

Viruses such as cytomegalovirus and Epstein bar virus have been found in the epidermis of vitiligo patients (Grimes et al. 1996). Additionally, HSV has been found to be associated with segmental vitiligo (Dwivedi et al. 2018). HIV infection has also been associated with vitiligo (Antony and Marsden 2003). Other skin-related disorders such as psoriasis and alopecia areata have been associated with viral infections (Gaurkar et al. 2014). Viral infections such as HCV, HBV, HSV have been associated with vitiligo (Dwivedi et al. 2018).

The possible mechanism by which viruses are involved in vitiligo pathogenesis is, however unclear. In the case of HIV, as it infects and decreases the $CD4^+$ T cells count, the infection could increase $CD8^+/CD4^+$ T cell ratio (Dwivedi et al. 2018), which has already been associated

with vitiligo. This increased CD8+ T cell number could lead to melanocyte destruction (Dwivedi et al. 2013b). Viral infections such as Herpes simplex virus, Epstein bar virus, cytomegalovirus through molecular mimicry and bystander activation can activate the innate immune response (Arango et al. 2013), which could then result in T cell- and B cell-mediated vitiligo pathogenesis (Table 1).

Persistent chronic viral infections like HIV, HCV, HBV, HSV have the ability to develop autoimmune vitiligo by constant activation of the immune response (Table 1) (Arango et al. 2013; Smatti et al. 2019). The constant activation may lead to an immune response against self-antigens resulting in melanocyte destruction (Table 1). The viral infection could also enhance the already present oxidative stress in the susceptible patients (Ivanov et al. 2016), which could then trigger autoimmune reactions (Table 1).

4.2.2.1. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and vitiligo

Emerging studies have suggested that coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 might contribute to various inflammatory and autoimmune diseases (Galeotti and Bayry 2020; McMillan et al. 2021; Liu et al. 2021). The studies suggest that COVID-19 patients develop various autoimmune conditions like Guillain-Barre syndrome, SLE, Kawasaki disease, autoimmune haemolytic anaemia and idiopathic thrombocytopenic purpura (Galeotti and Bayry 2020; McMillan et al. 2021). The virus may trigger the autoimmune response through molecular mimicry, bystander activation and cross-reactivity (Galeotti and Bayry 2020; McMillan et al. 2021). A previous study suggested that autoimmune reactions may be triggered against the ACE II receptor (McMillan et al. 2021). Studies have also found that patients develop a range of autoantibodies post COVID-19 (McMillan et al. 2021; Chang et al. 2021).

Although COVID-19 infection has been linked with autoimmune diseases (Galeotti and Bayry 2020; McMillan et al. 2021; Liu et al. 2021), studies assessing the casual link between COVID-19 and vitiligo are scarce. Studies have only focused on the impact of vitiligo and its treatment on COVID-19 progression (Sarkar and Nayak 2020; Xu et al. 2021; Post et al. 2021). The mechanistic aspect assessing if COVID-19 can trigger autoimmune vitiligo is lacking. Nevertheless, studies have suggested that severe COVID-19 is linked with increased levels of pro-inflammatory cytokines like IL-10, TNF-α, IFN-γ and IL-2 (Del Valle et al. 2020; Pérez-Cabezas et al. 2021), and earlier studies have reported the involvement of increased TNF-α,

IFN-γ in vitiligo pathogenesis (Laddha et al. 2012b; Dwivedi et al. 2013d; Singh et al. 2021). TNF-α and IFN-γ enhance the expression of ICAM-1 on melanocytes, contributing to their T cell-mediated destruction (Laddha et al. 2012b; Dwivedi et al. 2013d; Singh et al. 2021). Furthermore, IFN-γ inhibits melanin biosynthesis contributing to vitiligo development (Cai et al. 2019). Overall, it may be speculated that COVID-19 symptoms, treatments and medications through molecular mimicry, bystander activation and cross-reactivity might contribute to autoimmune vitiligo. Stress caused to vitiligo patients due to COVID-19 symptoms, treatments and medication may also play a role in development of the disease. Therefore, future studies must explore the relationship between COVID-19 and autoimmune vitiligo development.

4.2.3. Other microbes

Tinea corporis, a superficial fungal infection caused by various dermatophytes species like *Epidermophyton*, *Trichophyton* and *Microsporon*, has been shown to be associated with vitiligo (Parimalam et al. 2015; Rao 2015). Although the incidence of *Tinea corporis* in vitiligo is very rare, cases with dermatophyte infection encircling vitiligo have been reported (Parimalam et al. 2015; Rao 2015). The exact mechanisms for the association of dermatophyte infection and vitiligo are unclear. However, it may be that activated Langerhans cells during the dermatophyte infection could trigger a melanocyte-specific T cell response (Arango et al. 2013; Parimalam et al. 2015; Rao 2015). Apart from this, intestinal parasites such as Ascaris lumbricoides and tapeworm have also been shown to be associated with vitiligo (Mohd et al. 2019). To date, the role of fungal and parasitic species in vitiligo is unknown (Mohd et al. 2019).

5. The role of microorganisms in the management of vitiligo

5.1. The role of gut microbiota in vitiligo management

The gut microbiome comprises trillions of bacteria, fungi, and viruses (Khan and Wang 2020). Diversity is important for a healthy gut and dysbiosis in the gut microbiome is linked with several autoimmune diseases, including vitiligo (Ganju et al. 2016; Pittayanon et al. 2019). It is interesting to note that the gut microbiome, despite being away from the skin, has an influence on vitiligo development(Ni et al. 2020). Depending on the composition of the gut microbiome, it can induce pro-inflammatory or anti-inflammatory responses (Wu and Wu 2012). However, the detailed mechanism by which the gut microbiome exerts such distinct

responses is unknown (Vieira et al. 2014). Therefore, it is necessary to study the role of the gut microbiome in the autoimmune development of vitiligo as this may serve as a potent target for the treatment.

The mechanisms by which gut microbiota exert a disease protective role in unclear. Studies suggest it plays a crucial role in maintaining the intestinal epithelial barrier and forming a mucosal immune system against pathogens (Chelakkot et al. 2018). The healthy gut comprises the intact epithelial intestinal barrier, which reduces the translocation of bacteria via the mucosa (de Oliveira et al. 2017; Paetzold et al. 2019). Dysbiosis in the gut microbiota may lead to an altered intestinal barrier leading to the inflammatory response (Chelakkot et al. 2018). The condition has been particularly well documented as leaky gut hypothesis where the alteration in the gut barrier leads to translocation of lymphocytes from the gut to the liver resulting in autoimmune reaction in the liver (Mu et al. 2017a). Dysbiosis in the gut microbiome has been observed in various autoimmune diseases like IBD, irritable bowel syndrome (IBS), T1D, MS, SLE and vitiligo (Ganju et al. 2016; Mu et al. 2017a; Pittayanon et al. 2019). Therefore, it suggests that maintaining the intestinal barrier through the gut microbiota may serve as a potent therapeutic target for autoimmune diseases like vitiligo (Figure 2) (Table 2).

The gut microbiota produces metabolites that have an important role in reducing inflammation. Short-chain fatty acids (SCFAs) produced by the gut microbiome reduce inflammatory cell migration, adhesion and proliferation (Parada Venegas et al. 2019). It also reduces the production of pro-inflammatory cytokines (Parada Venegas et al. 2019). SCFAs also inhibit the critical inflammatory NK-kB pathway (Parada Venegas et al. 2019). The gut microbiota and skin microbiota-derived tryptophan has been shown to attenuate inflammation in atopic dermatitis patients (Yu et al. 2019).

An enhanced tryptophan pathway has been found in psoriasis patients (Harden et al. 2016). Other key metabolites like retinoic acid and polysaccharide A produced by *Clostridia* and *Bacteroides spp. s*uppress the immune response by inducing Tregs (Xiao et al. 2008; Russler-Germain et al. 2017). Previously, it has been found that there is a reduced abundance of *Clostridia* and *Bacteroides spp.* in vitiligo patients (Bzioueche et al. 2020), suggesting these metabolites may have a role in the pathogenesis of vitiligo. Therapeutic targets involving key metabolites produced by the gut microbiota may be a potent treatment option for vitiligo.

The gut microbiota has a crucial role in maintaining immune gut homeostasis (Wu and Wu 2012). Particularly, it maintains the balance between T helper 17 cells (Th17 cells) and Tregs (Wu and Wu 2012). However, studies evaluating the role of gut microbiota in vitiligo are lacking, though observational studies have found an alteration of gut microbiota in vitiligo patients (Ni et al. 2020; Lu et al. 2021). Notably, the *Bacteroidetes*: *Firmicutes* ratio was decreased (Ni et al. 2020). Furthermore, 23 serum metabolites were found to be altered in vitiligo patients (Ni et al. 2020). *Corynebacterium*, *Ruminococcus*, *Jeotgalibaca* and *Psychrobacter* were found to be correlated with disease duration and inflammatory markers like IL-1β (Ni et al. 2020). Similar observations have been observed in skin diseases like psoriasis (Stehlikova et al. 2019). The findings suggest the alteration in the gut microbiome can induce an inflammatory response in vitiligo patients.

In a healthy gut, the microbiota plays a crucial role in the induction, development, and function of Tregs (Wu and Wu 2012). For instance, *Bifidobacterium* and *Lactobacillus* enhance Treg function (Sun et al. 2020). *Bacteroides fragilis* produce metabolites like polysaccharide A, which induces Tregs through the TLR2 pathways (Kayama and Takeda 2014). Previous studies have suggested the role of impaired Treg cell function and number in vitiligo pathogenesi s(Giri et al. 2020b, 2021). Specifically, impaired NFATc1 and FOXP3 expression leads to decreased Treg suppressive function and to decreased expression of immunoregulatory genes (IL-10, TGF-β and CTLA-4) (Giri et al. 2020b, 2021). The gut microbiota can also serve as a potent therapeutic target for vitiligo as the metabolites like SCFAs (?) produce enhanced epigenetic regulation of FOXP3 (Sharma et al. 2020). *Lactobacillus casei* DN 114001 has been shown to activate NFATs in BALB/c mice (Azad et al. 2018). Therefore, the gut microbiome can serve as a vitiligo therapeutic modulating the expression of NFATs and FOXP3, the key transcriptional regulators of Tregs. In addition, gut microbiome-induced Tregs may be a potential therapeutic target for vitiligo (Figure 2) (Table 2) (Giri et al. 2020b).

Given the crucial role of the gut microbiome in autoimmune diseases like vitiligo, there exists an opportunity to intentionally modulate the gut microbiome for therapeutic purposes. The potential therapeutic options to restore the gut microbiome for the treatment of vitiligo are discussed in the next sections.

5.2. Role of probiotics in management of vitiligo

Probiotics are beneficial microbes to the host as they maintain immune homeostasis in the gut by enhancing the mucosal barrier, modulating the immune response, and inducing antimicrobial response (Hemarajata and Versalovic 2013). The metabolites produced by these probiotics shape a healthy gut microbiome by suppressing pathogenic microorganisms(Hemarajata and Versalovic 2013). Several human and animal model-based studies have suggested the beneficial role of probiotics in the suppression of autoimmune diseases like RA, T1DM, SLE(Dol pady et al. 2016; Bodkhe et al. 2019; Khorasani et al. 2019). Moreover, probiotics have been suggested to impart beneficial effects in the treatment of several skin diseases like atopic dermatitis and psoriasis (Bindurani and Bindurani 2019). Studies have suggested that *Lactobacillus* spp. (*L. casei, L. rhamnosus, L. plantarum*), *Bacillus lactis, Fructooligosaccharide*, and *Galactooligosaccharide* suppress autoimmune skin diseases like AD (Ibáñez et al. 2018). Furthermore, *Bifidobacterium infantis* administered into psoriatic patients reduces C-reactive proteins and suppresses TNF-α and IL-6 production (Groeger et al. 2013). These studies suggest probiotics may serve as a potent therapeutic agent for vitiligo treatment as well.

The underlying mechanisms involved in probiotic-based therapeutics of vitiligo are not known, but studies suggest that probiotics can induce the production of anti-inflammatory cytokines like TGF-β and IL-10 (Azad et al. 2018). Probiotics can bind to DCs, leading to DC-mediated activation of Treg cells (Foligne et al. 2007; Xiao et al. 2018). They also suppress the key inflammatory pathways like MAPK and NF-κB, leading to reduced levels of IL-1β, IL-6 and TNF-α (Llewellyn and Foey 2017). Additionally, probiotics produce adenosine that is capable of suppressing Th1 and Th17 cell subsets and promoting Treg cells (Omenetti and Pizarro 2015).

Our previous study has suggested altered NFATc1 and FOXP3 results in suppressed Treg cells, which leads to vitiligo pathogenesis (Giri et al. 2020b). Probiotics can enhance expression of NFATs and FOXP3, the key transcription regulators of Tregs, and SCFAs produced by probiotics leads to epigenetic regulation of FOXP3 expression (Sharma et al. 2020). The probiotic *Lactobacillus casei* DN 114001 from fermented milk has been shown to activate NFATs in the BALB/c mouse model (Azad et al. 2018). Additionally, there is a role for *Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus reuteri, Bifidobacterium* and *Streptococcus thermophilus* in the induction of CD4+CD25+FoxP3+ Tregs (O'Mahony et al. 2005, 2008; Whorwell et al. 2006; Feleszko et al. 2007; Kwon et al. 2010; Lavasani et al. 2010;

Konieczna et al. 2012; Kim et al. 2014). The above probiotics have been linked with increased Treg suppressive capacity enhancing the production of IL-10 and TGF-β, the Treg-associated suppressive cytokines (O'Mahony et al. 2005, 2008; Whorwell et al. 2006; Feleszko et al. 2007; Kwon et al. 2010; Lavasani et al. 2010; Konieczna et al. 2012; Kim et al. 2014; Dwivedi et al. 2015). The role of prebiotics fructo-oligosaccharides, inulin, resistant starch, B-galactooligosaccharides in suppression of autoimmune diseases by promoting Tregs number and suppressive capacity has also been shown. The therapeutic potential of probiotics and prebiotics in Treg-mediated treatment of vitiligo and other autoimmune diseases has also been suggested (Figure 2) (Table 2) (Dwivedi et al. 2015, 2016).

5.3. Faecal microorganism transplantation (FMT)

Apart from probiotics-based treatment strategies, FMT can be employed for the restoration of the gut microbiome, which could lead to novel therapeutic options for the treatment of autoimmune vitiligo(Gupta et al. 2016). However, studies examining the therapeutic potential of FMT in vitiligo are lacking. Studies have been carried out in psoriasis. The treated patient showed significant improvement after five weeks, suggesting FMT must also be studied for the treatment of autoimmune diseases like vitiligo (Figure 2) (Table 2) (Chen et al. 2020). The outcome of FMT can be influenced by various factors like host genetics, host immune response, bacterial load and composition, route and mode of administration. Therefore, detailed studies examining the safety and efficacy of FMT-based vitiligo treatments are warranted.

6. Future directions

Limited studies exploring the role of microorganisms in vitiligo pathogenesis have shed light on the involvement of microorganisms in vitiligo. The dysbiosis in the skin and gut microbiome have suggested the involvement of microbes in the pathogenesis of vitiligo. Furthermore, *in vivo, in vitro*, and human clinical trials have examined the role of probiotics in the treatment of various autoimmune diseases. Although the studies suggest probiotic treatments as safe and efficacious in the treatment of autoimmune disease, the lack of studies in vitiligo begs the question of its safety and efficacy in vitiligo therapy. Future studies must focus on finding the exact mechanism involved in microorganism-mediated pathogenesis of vitiligo and study the safety and efficacy of probiotic-based therapeutics for vitiligo.

7. Conclusions

Overall, the studies suggest the decrease in microbial diversity i.e. commensal microbes comprising the skin microbiome could lead to a breach in the skin immune barrier resulting in autoimmune vitiligo. Additionally, the increase in the pathogenic microbes in the lesional skin could trigger an innate immune response through various mechanisms like superantigen formation, molecular mimicry, bystander activation, constant activation. The activated innate immunity could result in T cells and B cells activation, which thereby could cause melanocyte destruction leading to vitiligo pathogenesis. Studying the host-microbiome relationship and identifying the particular skin-associated microbes and the pathways involved in the initiation and exacerbation of immune response against melanocytes could lead to novel immunotherapies for the treatment of vitiligo.

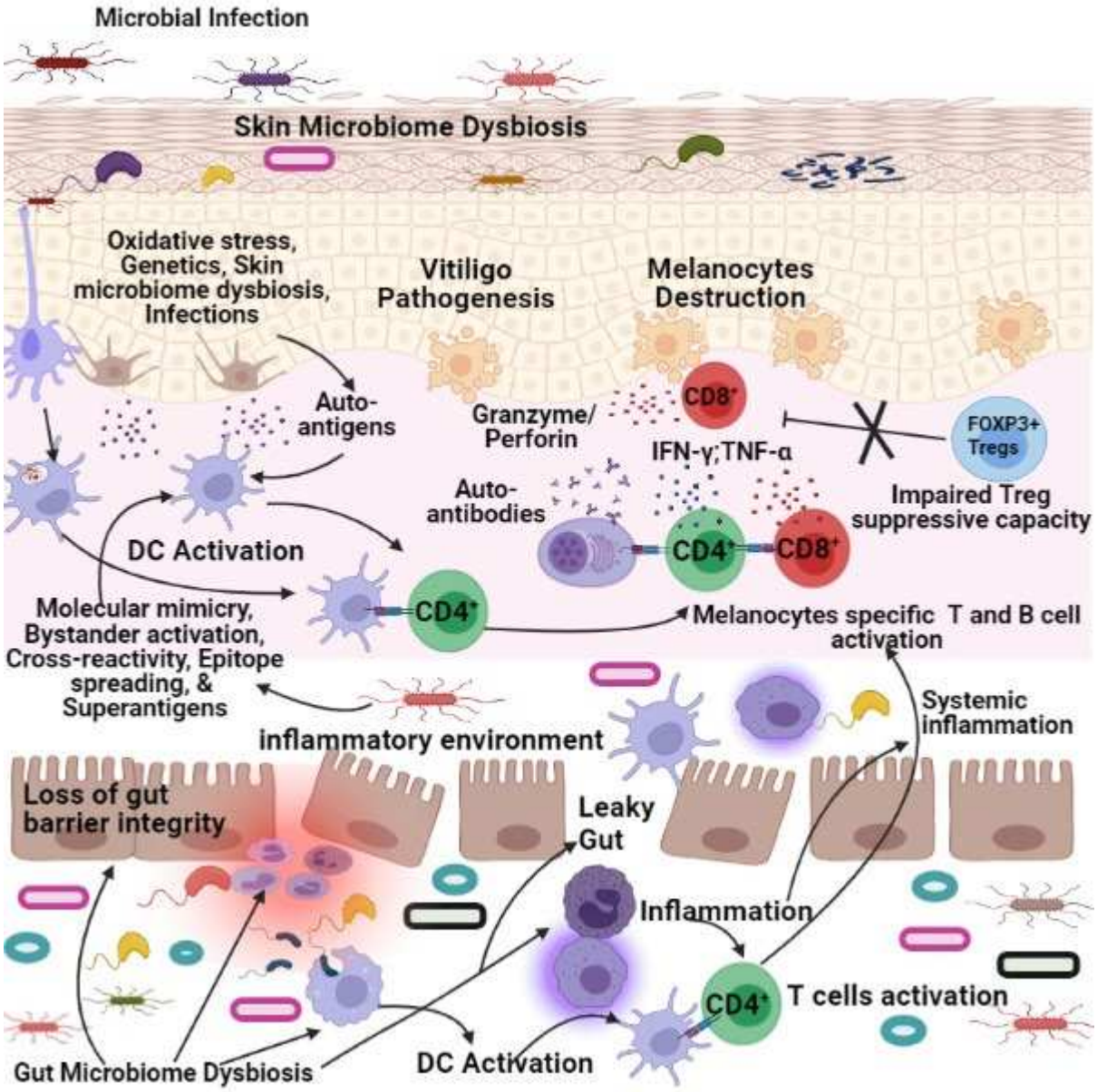

Figure 1: Role of microorganisms in vitiligo pathogenesis

Multiple factors such as infections, environment, genetics, oxidative stress, altered melanocyte adhesion triggers vitiligo development. In particular, infections, dysbiosis in skin and gut microbiome, through molecular mimicry, bystander activation, cross reactivity, epitope spreading and superantigen formation, leads to activation of dendritic cells which thereby activates melanocyte specific T and B cells. Additionally, oxidative stress leads to production of self-antigens, which further activate melanocyte specific T and B cells. These melanocyte-specific $CD8^+$ and $CD4^+$T cells produce perforin, granzyme B, IFN-γ, whereas B cells produce autoantibodies that contribute to melanocyte destruction. The decreased immunosuppressive

capacity of Tregs, leads to unchecked $CD4^+$ and $CD8^+$ T cells and B cells, further contributing to melanocytes death leading to vitiligo pathogenesis.

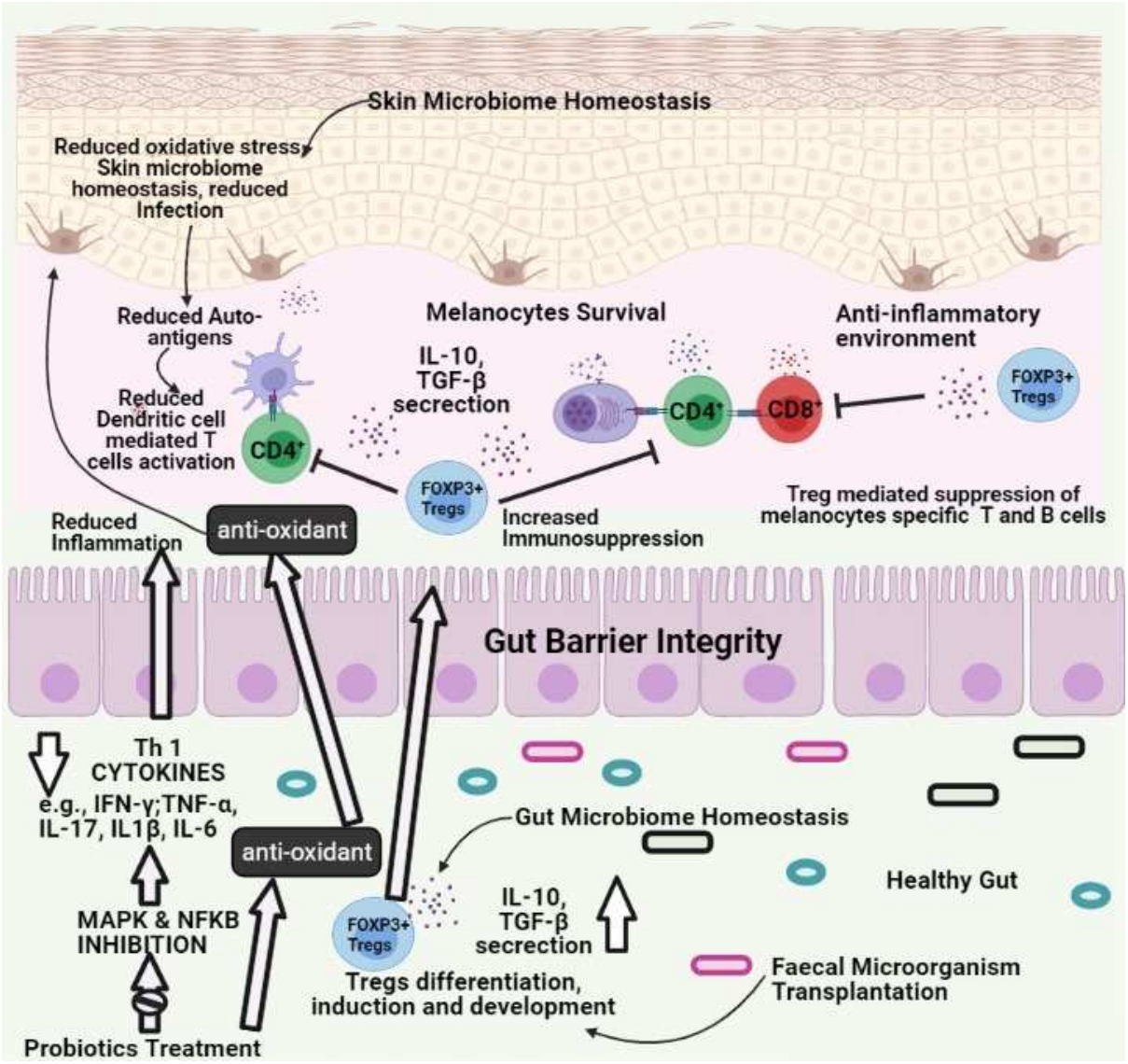

Figure 2: The proposed mechanism of microbiome associated management of vitiligo.

The probiotic treatment faecal microorganism transplantation (FMT) maintains gut microbiome homeostasis and gut barrier integrity. The healthy gut thus reduces infections and further reduces dysbiosis in the skin microbiome. The probiotics and FMT suppress autoimmunity by promoting Treg cells induction, development and function. Probiotics also inhibit inflammatory responses by blocking MAPK and NFKB pathway, suppressing Th1 cell subsets and IFN-γ, TNF-α, IL-17, IL1β, and IL-6 cytokine production. Probiotic treatment decreases anti-oxidants which can reduce oxidative stress in melanocytes resulting in decreased dendritic cell-mediated melanocyte-specific T and B cells activation. The enhanced Treg cells

produce increased anti-inflammatory cytokines IL-10 and TGF-β, which may suppress melanocyte-specific T and B cell-activation leading to melanocyte survival.

Table 1: The role of microorganisms in vitiligo pathogenesis

Microorganisms/Viruses	Mechanism of vitiligo pathogenesis	References
Methylobacteriumm, Enhydrobacter, Paracoccus, Streptococcus, Staphylococcus, Anaerococcus, Microbacterium, Streptophyta and *Nocardiodes, Skermanella, Novosphingobium, Roseomonas, Cellvibrio, Turicibacter, Erysipelotrichaceae* and *Erysipelotrichales*	*Methylobacteriumm, Enhydrobacter, Paracoccus, Streptococcus* and *Staphylococcus* are found in the lesional skin. *Anaerococcus, Microbacterium, Streptophyta* and *Nocardiodes, Actinobacteria* and *Proteobacterial, Firmicutes* are predominant in the lesional skin. 39 taxa found to be different between the lesional and non-lesional skin, specifically, *Skermanella, Novosphingobium, Roseomonas, Cellvibrio, Turicibacter, Erysipelotrichaceae* and *Erysipelotrichales* Dysbiosis in the skin microbiome and a decrease in microbial diversity in the lesional skin could hamper the protective skin barrier, aggravating vitiligo.	(Ganju et al. 2016)
Alkaliphilus, dysgonomonas, Odoribacter, Oscillospira, Pedobacter, Parabacteroides Ruminococus, Pseudomonas aeruginosa and *Bacteroides vulgatus*	Antibiotic treatment has shown to result in a decrease in microbial diversity resulting in increased B cell and T cell activity contributing to melanocytes destruction and vitiligo pathogenesis.	(Dellacecca et al. 2020)

Gut Microbiome	Reduced *Cutibacterium, Proteobacterium, Gammabacterium, Acintobacter* and *Paracocus* in lessional skin. Dysbiosis in gut microbiota as a result of lowered diversity in vitiligo patients, whereas *Firmicutes* and *Bacteroidetes* fraction increased in gut. *Bifidobacterium* decreased in lesional skin. *Enterococcus, Mycoplasma, Veillonella, Intestinibacter, Bacteroides, Escherichia-Shigella, Parabacteroides, Bifidobacterium,* and *Streptococcus* increased in non-lesional skin. Microbial changes in the skin and gut microbiome leads to activation of the innate immune response and increased pro-inflammatory cytokines like IFN-γ, and chemokines such as CXCL9, CXCL10 and CXCL16. These increase activation and trafficking of $CD8^+$ T cells to vitiligo lesions.	(Ni et al. 2020; Bzioueche et al. 2020)
Helicobacter pylori, Epstein bar virus, cytomegalovirus	*Helicobacter pylori*, Epstein bar virus, cytomegalovirus may play a role in the development of vitiligo through molecular mimicry.	(Doğan et al. 2014; Dwivedi et al. 2018)
Legionella pneumophila, Chlamydia trachomatis, Listeria monocytogenes, and lipopolysaccharides of various microorganism	Through bystander activation of self-reactive T cells, B cells, NK cells and DCs, *Legionella pneumophila, Chlamydia trachomatis, Listeria monocytogenes,* and lipopolysaccharides of various microorganism can lead to vitiligo development.	(Fujinami et al. 2006; Arango et al. 2013; Jung et al. 2017;

		Dwivedi et al. 2018; Pacheco et al. 2019)
Mycobacterium leprae	*M. Leprae* infection can cause cross-reactivity or epitope spreading against melanocytes, leading to vitiligo pathogenesis.	(Dupin et al. 2003; Oyarbide-Valencia et al. 2006)
Hepatitis C virus, Hepatitis B virus, and HIV	Persistence of infections like hepatitis C virus, hepatitis B virus, and HIV in vitiligo patients may trigger autoimmunity as a result of constant activation of the immune response.	(Antony and Marsden 2003; Dwivedi et al. 2018)

Table 2: The role of microorganisms in vitiligo management

Microorganisms/Probiotic strains	Key findings	References
Clostridia and *Bacteroides spp.*	Production of retinoic acid and polysaccharide A suppresses the immune response by inducing Tregs.	(Xiao et al. 2008; Russler-Germain et al. 2017)
Bacteroides fragilis	*Bacteroides fragilis* produces metabolites like polysaccharide A, which induces Tregs through the TLR2 pathways.	(Kayama and Takeda 2014)
Bifidobacterium and *Lactobacillus*	*Bifidobacterium* and *Lactobacillus* enhance Treg function.	(Sun et al. 2020)
Lactobacillus helveticus HY7801	Administration induces regulatory CD11c+ dendritic cells, which reduces pro-inflammatory cytokines TNF-α, IFN-γ, and IL-17A and enhances anti-inflammatory cytokine IL-10 production by CD4+ T cells.	(Kim et al. 2015)
*Lactobacillus kefiranofaciens*and *Lactobacillus kefiri*	Administration increases IL-10 levels, which inhibits the secretion of pro-inflammatory cytokines TNF-α, IL-1β, IL-2 and IL-6.	(Wei et al. 2015)
Lactobacillus casei DN 114001	*Lactobacillus casei* DN 114001 activates NFATs in BALB/c mice, which increases Treg cell suppressive function.	(Azad et al. 2018)
Lactobacillus rhamnosus, *Lactobacillus delbrueckii*	Treatment enhances Tregs and the increases expression level of Foxp3. Decreases IL-6, IFN-γ, IL-17 and RORγt levels.	(Khorasani et al. 2019)

	Reduces Th1-Th17 cells.	
Lactobacillus rhamnosus GR-1 and *Lactobacillus reuteri* RC-14	Treatment leads to significant reduction of pro-inflammatory cytokines TNF-α, IL-1β, IL-8, IL-6, IL-12, IL-15, IL-17 and M1P-1α.	(de los Angeles Pineda et al. 2011)
Lactobacillus paracasei GMNL-32, *Lactobacillus reuteri* GMNL-89 and *Lactobacillus. reuteri* GMNL-263	Supplementation in NZB/W F1 mice reduces the expressions of IL-1β, IL-6 and TNF-α by suppressing the mitogen-activated protein kinase and NF- κB signalling pathways. Increases the differentiation of CD4+CD25+FoxP3+ T cells.	(Hsu et al. 2017; Tzang et al. 2017; Yeh et al. 2020)
Lactobacillus oris, Lactobacillus rhamnosus, Lactobacillus reuteri, Lactobacillus johnsonii, and *Lactobacillus gasseri*	Lactobacillus treatment contributes to an anti-inflammatory environment by decreasing IL-6 and increasing IL-10 production in the gut. Skews the Treg-Th17 balance towards a Treg phenotype.	(Mu et al. 2017b)
Lactobacillus casei, Lactobacillus acidophilus	Oral administration reduces IL-12, IL-6, TNF-α, IL-1β, IL-17 and IL-4 levels and increases anti-inflammatory cytokine IL-10. Reduce oxidative stress. Reduced inflammation, decreased oxidative stress and reduced anti-inflammatory cytokines may suppress anti-melanocyte-specific T and B cells.	(So et al. 2008; Amdekar et al. 2013; Alipour et al. 2014)
Oral administration of *Escherichia coli* Nissle 1917	Decreases inflammatory cytokines such as IFN-γ, TNF-α and IL-17, Increases production of autoreactive CD4+ T cells, IL-10 and CD4+ Foxp3+ in lymph nodes. Improves intestinal barrier dysfunction and neuroinflammatory	(Secher et al. 2017)

	factors.	
Faecal microorganism transplantation	Shown to be beneficial in treatment of psoriasis, an autoimmune skin disease similar to vitiligo.	(Gupta et al. 2016; Chen et al. 2020)

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