International Journal of
Science Inventions Today
www.ijsit.com
ISSN 2319-5436
Review Article

PATHOGENESIS OF ROSACEA: A REVIEW ON CLINICAL BASIS

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ABSTRACTS

Rosacea is a commonly encountered chronic inflammatory skin disease with a predilection for highly visible areas of the skin such as the face. The cosmetic symptoms of Rosacea can be substantial and may greatly reduce a patient's quality of life. Although there is no definitive cure for Rosacea, effective treatment of symptoms can mitigate the deleterious effects of this condition and improve quality of life. In this article, we review both existing and emerging cosmetic treatments for Rosacea, including topical medications, systemic pharmacologic therapies, light-based modalities, and procedural interventions, and assess their ability to improve the cosmetic symptoms of Rosacea.

Keywords: Rosacea, skin disorders, genetic predisposition, pharmacological therapy.

INTRODUCTION

Rosacea is a common cutaneous vascular skin disorder that typically occurs in adults and affects highly visible areas of the skin such as the face.(1). It is characterized by papules and pustules often associated with erythema and flushing. In the most severe cases, the skin can thicken and enlarge (phymas), usually on and around the nose (1, 2). Additional secondary features burning or stinging elevated red plaques, skin dryness, ocular manifestation and circumscribed or diffuse edema may be present.

Prevalence & Associated Factors:

Rosacea can occur in anyone, it most prevalent in middle-aged women than men, although in men the condition tends to be more severe. Rosacea is a condition that most commonly affects individuals with fair skin, blue eyes, and blond hair. Afro- Asian population is comparatively less affected (3). The symptoms typically begin between 30 and 50 years of age (4). Gender predisposition mainly depends on the specific subtype of Rosacea, the development of rhinophyma predominantly occurs in male patients(5). Although environmental factors are responsible for the development of Rosacea, there is also genetic susceptibility. Three HLA (human leukocyte antigen) alleles, all MHC class II proteins are significantly associated with Rosacea particularly HLA-DRB1, HLA-DQB1, and HLA-DQA1(6).

Classification:

Rosacea is a complex skin disorder, it has been classified into four subtypes and one variant(7, 8).

1. Erythematotelangiectatic Rosacea: persistent central facial erythema +/_ telangiectasia. Flushing, burning, stinging.

2. Papulopustular Rosacea: Papules and pustules (no black or whiteheads). Transient/Persistent facial erythema usually on the central face.

3. Phymatous Rosacea: Commonly affect nose, chin, forehead, ears. Marked thickening of the skin especially nose (Rhinophyma). Hypertrophy of sebaceous glands and connective tissue.

4. Ocular Rosacea: Frequently undiagnosed. Foreign-body sensation with dry eyes, burning and blurred vision. The severe form can lead to blindness and inflammatory keratitis

Variant Granulomatous Rosacea: Small red-brown papules on forehead, cheeks and perioral region. On diascopy, the monomorphic papules show apple-jelly like color.

Pathogenesis:

The precise pathophysiology of Rosacea has not yet been completely identified, most agree that it is a multifactorial etiology (9, 10). Over the years, many suspected but unconfirmed cases have been reported. These include genetic predisposition, dysregulation of the cutaneous innate and adaptive immune system, vasoactive and neurocutaneous mechanisms, climatic and ultraviolet(UV) exposure, pilosebaceous unit abnormalities, local inflammatory responses to cutaneous microorganisms, as well as vascular abnormalities and lymphoid vessels seem to play a role(11, 12). Also, various triggers can aggravate Rosacea these include heat, alcohol, caffeine, spicy or hot foods, stress. Here, we review the genetic predisposing factor for Rosacea,

vascular changes and innate and adaptive immune response in Rosacea along with triggering factors. Finally, we will discuss neurovascular abnormalities in Rosacea. Figure 1.

Genetic Predisposition .Glutathion S-Transfersae .SNPs intergenic between HLA-DR & BTNL2	**Innate & Adaptive Immunity Dysfunction** .Epidermal barrier disruption .TLR-2 & klk-5 .LL-37 .Vit D & .T cell mediated Responses mediated Responses
Environmental Triggering Factors .Microbial Agents .UV irradiation .Stress .Alcohol .Heat	**Dysregulation in Neurocutaneous Mechanisms** .PACAP/VIP .Substance P .CCRP

ROSACE

Figure 1: Schematic view of the factors contributing to the pathogenesis of Rosacea

Genetics of Rosacea:

It has been long thought that genetics plays a substantial role in Rosacea, but this is unproven yet. The truth, of course, is that no one knows the real cause behind the Rosacea and with that being the case, a considerable amount of research has gone into it. Current studies in twins clarify that genetics accounts for approximately 50% of the contribution to the disease (13). Although environmental factors contribute to the development of Rosacea such as sun exposure, temperature changes (heat and cold), alcohol, caffeine, spicy or hot foods strong emotions and stress account for the remaining 50%. In a genome-wide association, two single nucleotide polymorphisms (SNPs) were discovered, rs763035 and rs111314066 that are significantly associated with Rosacea (6). Besides, genetics polymorphism in the glutathione S-transferase (GST) genes was found to be associated with increased disease risk. GST encodes an enzyme that is responsible for cellular defense against reactive oxygen species (ROS) damages in Rosacea patients. These studies strengthen the hypothesis of genetic components. Interestingly, found that genetics and environmental factor contribute equally to the disorder. However, recent molecular studies in different clinical manifestations indicate a marked up-regulation of genes that are involved in vasodilatation (Rosacea).

Vascular Hyper-activity:

Several blood vessels in the facial region or there is damage to the facial blood vessels. The facial vessels swell or become inflamed, leading to vascular constriction of the facial vessels. There are several contributing factors like heat, cold, alcohol, ultraviolet radiation, emotions, and hot drinks, spicy foods that

influence the skin of the face and cause blood vessels to contract and dilate. Flushing after hot liquids such as water, coffee or tea is due to pharyngeal heating of the blood that perfuses the hypothalamus through the exchange of countercurrent heat that affects the jugular vein and the common carotid artery. Hyperthermia in patients with Rosacea causes a decrease in the blood supply from the face to the brain. The dysfunction seems to be a microcirculatory alteration of the facial angular veins (Vena facials sive anglularis) that are associated with the cerebral vascular cooling system. This can lead to venous congestion and thermoregulation failure. The facial veins of the face help in drain the parts of the face that are most affected by Rosacea, including conjunctiva. This can explain the frequent involvement of the eyes. A vascular dysfunction may be the cause of increased migraine headaches in Rosacea patients. Rosacea skin responds in a normal way to several vasoactive substances like caffeine or chemo-mediators such as epinephrine, acetylcholine or histamine. Vasoactive intestinal peptide (VIP) and its receptors are critical for the blood flow regulation. These receptors were found in higher concentrations in rhinophyma and, therefore, it is suggested that this may cause vascular and dermal changes in Rosacea.

Innate Immunity and Cathelicidin antimicrobial peptide: potential role in Rosacea:

Rosacea might be caused by an overactive or excessive inflammatory immune response. Human skin function as a barrier and provide defense against invading organism via the various innate immune system and epidermal skin barrier enhances the susceptibility of the skin toward specific environmental stimuli such as toxins, temperature changes, and endogenous mediators. The innate immune system of the skin is programmed to detect microbes and tissue damage. In innate immunity, the pattern recognition system, which includes the Toll-like Receptor (TLR) families, responds to physical and environmental stimuli such as UV, microbes, and injury. Stimulation of the innate immunity typically prompts a controlled increase in cytokines and antimicrobial peptides [AMPs] in the skin. Cathelicidins are part of the innate immune system and one of the first antimicrobial peptides [AMPs] identified in mammalian skin(14). Few forms of cathelicidin peptide have an extraordinary ability to be both vasoactive and proinflammatory. People with Rosacea have an abnormal amount of cathelicidin in epidermis compared with those present in normal individuals. These forms of cathelicidin peptides induce inflammation and vascular changes, while the types found on normal skin function as antibiotics and have little to no inflammatory action(15). One of the most common forms of cathelicidin is LL-37 that plays a central role in the pathogenesis of Rosacea. LL-37 has an antimicrobial activity that (not only) kills pathogens (but also alters the host immunity by promoting leukocyte chemotaxis) as well as immunomodulatory and angiogenetic properties. Patients with Rosacea exhibit a specific pattern and increased levels of cathelicidin peptide (LL-37) due to abnormal production of local serine protease kallikrein-5 (stratum corneum tryptic enzyme). The usually high level of the serine protease kallikrein-5 (KLK5) is responsible for the production of cathelicidin precursor molecules to form the active antimicrobial peptide LL-37. The up-regulation of cathelicidin LL-37 promotes skin inflammation and vascular changes. The increased cathelicidin production and high protease activity are caused by activation of vitamin D3 via UV, by stress in endoplasmic reticulum and TLR2. Figure 2. The Toll-like receptors function as a sensor for the skin, whose well-

known role is to promote inflammation. Skin must have the ability to detect dangerous stimuli such as injury, infection or damage of the extra-cellular matrix. Among various detection systems, TLRs are an extreme and powerful component that generally recognizes microorganism derivatives and prompts cell reactions, for example, cytokines and anti-microbial peptides. In the skin of the people with Rosacea, TLR2 expression is very high as compared to non-influenced individuals (16). The high expression of TLR2 increases the skin susceptibility to the environmental triggers (UV, heat) and eventually increases cathelicidin peptide LL-37 production in the epidermis. The involvement of TLR2 in Rosacea skin causes high cathelicidin and KLK5 expressions. The elevated epidermal serine protease activity results in processing forms of cathelicidin peptides to peptides that are inflammatory and antigenic and induce typical symptoms of Rosacea I.e. inflammation, erythema, telangiectasia, and vascular changes.

Role of Adaptive Immunity:

In addition to the innate immunity, the adaptive immune system seems to play a role in different types of Rosacea. Little is known about the adaptive immune system in Rosacea. Occasionally, activation of T and B-cells, a significant increase in CD4+ cells over CD8+ cells suggest that cell-mediated immune responses have an important role in the pathogenesis of the disease cell responses are dominated by T helper type 1 and type 17(Th1/Th17) cells, resulting in several inflammatory cytokines such as TNF-α, INF-ɣ or IL-17. An up-regulation of IL-17 induces angiogenesis via VEGF and also affects LL-37 expression in humans. Thus, Th17 cytokines may affect the abnormal expression of LL-37 as observed in patients with Rosacea. it was found that the expression of the chemokine interleukin-8 (CXCL8, a major Neutrophil Chemotactic factor), CXCL-1, CXCL-2 and CXCL-6 were also significantly up-regulated in Rosacea patients(17). Increased antigenic characteristics of these chemokines in patients with Rosacea attract Neutrophil and Th17 cells into the inflammatory tissue. So far, the role of B cells is underestimated as a causative agent of Rosacea compared to T cells. However, about 10% to 20% of inflammatory cell infiltration in Rosacea consists of CD20+ B cells. Also, the infiltration of plasma cells with increased anti-nuclear antibody titers(18) are commonly found in patients with Rosacea. These results indicate that the B-cell mediated immune response in Rosacea requires further consideration. However, it can be concluded that patients with Rosacea exhibit activation of the adaptive immune system with a predominantly Th1 response, even at the onset of the inflammatory response.

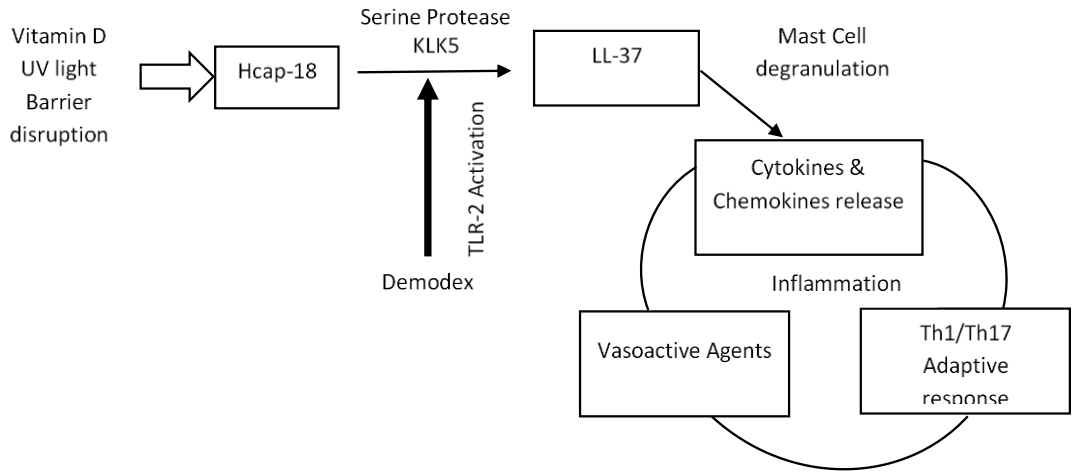

Figure 2: Innate and Adaptive immune dysfunction in Rosacea

Microbial agents: Demodex folliculorum, B. Oleronius, H. pylori:

Demodex miles are considered to be normal skin flora and found in human hair follicles, sebaceous glands, and meibomian glands. There are two species of Demodex- Demodex follicular, which live in hair follicles on the face commonly near the nose, cheeks, forehead and Demodex brevis, which live in hair follicles of the eyelid, eyelashes. In the past, it has been considered innocuous but recent evidence suspects that these mites play a role in the pathogenesis of Rosacea. Studies have shown that the density of Demodex mites is significantly increased in the facial skin of the patient with Rosacea as compared to someone with normal skin (19-21). When an individual is subjected to a large amount of infection with Demodex, then the infestation is known as demodicosis. Demodex in the eye can cause inflammation, infection and blurred vision.

When the epithelial barrier is disturbed the Demodex mites act as a pathogen and penetrates the dermis and promotes an inflammatory response from keratinocyte by stimulating toll-like receptor 2 (TLR2)(22). Furthermore, the inflammation might also be aggravated when dead mites release their product, which may further induce Neutrophil chemotaxis. Chemokines such as IL-8 and TNF-α, in turn, attract more Neutrophil and thereby exacerbate inflammation. Activated Neutrophil induces the release of cathelicidin which leads to tissue damage. There is also genetic susceptibility that effects tissue compatibility, the presence of antigen HLA CW2 and CW4 may decrease the immune performance and increase the survival of Demodex mites.

In addition to Demodex mites, gram-negative bacteria bacillus Polonius have been isolated from a patient with Rosacea patient shows increased seroreactivity to B. Polonius protein that stipulates TLR-2, which suggest that this microorganism induces immune responses and onset of Rosacea symptoms. Helicobacter pylori infection in the etiology of Rosacea has been controversial for a long period of time. But recent studies provided enough evidence that H.pylori is possible factor in the development of Rosacea symptoms. A high

prevalence of H.pylori infection in Rosacea patients than in controls has been noted in different studies (23). However, in controlled studies, sometimes the prevalence rate is equal to controls and sometimes higher than controls. H.pylori is a bacterium that lives in the intestinal lining of the stomach and releases a protein called Bradykinin. Increased plasma level of Bradykinin and H.pylori induced ROS was found to be associated with vasodilatation and inflammation in Rosacea. In controversial, different studies do not provide a critical contrast between Rosacea and control. In a double-blind controlled study on the effect of destroying H.pylori in those with both, Rosacea and H.pylori, the overall rating score for Rosacea was found to be unhelpful. A study in South Korea found that Helicobacter pylori may be the leading cause of Rosacea, but it has not been clarified yet and further research is needed to confirm this association.

Ultraviolet (UV) radiation and dermal matrix degradation:

Several studies have provided information about the harmful effect of ultraviolet (UV) radiation on human health especially on Rosacea and psoriasis are known to be associated with dermal remodeling after UV irradiation. Prolonged ultraviolet A (UVA) irradiation increases the activity of metalloproteinase MMP—1, which contributes to the collagen degradation in the dermis as seen in Rosacea. The hallmark of Rosacea is solar elastosis, which is one of the typical Histopathological findings in Rosacea, has been observed after prolonged UV exposure. Furthermore, in cultured keratinocyte, irradiation of the skin with UVB up-regulates the expression of vascular endothelial growth factor (VEGF), a potent androgenic factor, leads to dermal accumulation of cytokines and other inflammatory mediators that result in dermal matrix impairment.

However, the specific UVA and UVB wavelength that is most involved in triggering Rosacea is not clear yet. UV light exposure of the skin increases oxidative stress leading to an inflammatory reaction. UV irradiation is an important source in the production of ROS. The increased level of ROS has been noted in the skin of patients suffering from Rosacea compared to unaffected skin (24, 25). ROS promotes pro-inflammatory effects in the skin. Activated inflammatory response, pro-inflammatory cytokines, and other inflammatory mediators induce the expression of chemokines in keratinocyte. UVA irradiation enhances the effect of inflammatory chemokines, notably CXCL8, which reveals the activation of the TH1/Th17 pathway and recruitment of Neutrophil. It has also been reported that irradiation with UVA produces a decrease in the levels of antioxidants. Moreover, an increase in serum peroxide and decreased tissue superoxide dismutase activities were observed in patients with Rosacea after UV exposure, demonstrating that imbalance between oxidant and antioxidant pathways leads to pathological changes in the skin. A recent study of human keratinocyte suggests a prominent role of "myeloid Differentiation Factor 88" (MyD88) after UV irradiation MYD88 is an important adopter molecule for TLR signaling that regulates the UV induced MMP-1 and IL-6and is over expressed after chronic UV exposure. UV irradiation also induces ER stress in human epidermis. UV induced stress activates the PERK pathway. PERK activation results in enhanced expression of activating transcription factor 4 (ATF4), which is a major ER stressor. ATF4 activation promotes TLR2 expression during ER stress (26), thereby inducing angiogenesis, lymph angiogenesis. Thus UV mediated stress arguments innate immunity-enhancing inflammatory and antimicrobial response in Rosacea. These findings propose that alteration of the vasculature

and dermal grid by VEGF, FGF2 and MMP-1 and the generation of ROS and ER stressors after UV exposure give evidence that UV lights play a major role in Rosacea development.

Vitamin D3 or cholecalciferol:

Serum vitamin D levels were found to be low in much cutaneous inflammatory skin diseases such as psoriasis and atopic dermatitis as compared to healthy people. On the other hand, in patients with Rosacea, serum vitamin d level was very high than those of healthy individuals(27). Therefore, the pathogenesis of Rosacea seems to vary to some degree from that of other chronic cutaneous inflammatory disorders. Vitamin D is a secosteroid that helps the body absorb calcium and phosphate, maintaining strong bones. Some evidence suggests its involvement in modulating the immune system via regulating the innate and adaptive immunity, both of which are crucial for the pathogenesis of the inflammatory disorder. Vitamin D is a potent inducer of cathelicidin peptide LL-37. As discussed earlier, people with Rosacea have an abnormal amount of Cathelicidins in the epidermis as compared to normal individuals. Now it is clear that the increased cathelicidin production is caused by the activation of vitamin D3 via UV. Besides, vitamin D has been shown to increase the expression of TLR2 and KLK5 (28). The high expression of TLR2 and KLKS and LL-37 increases the skin susceptibility to the environmental triggers and subsequently stimulates the release of pro-inflammatory cascades such as cytokines, AMPs, and ROS that can alter the immune system.

Neurovascular Dysregulation in Rosacea:

Flushing and burning in facial skin is a common uncontrolled feature of Rosacea and is believed to be caused by the neurovascular disorder. In addition to inflammation, abnormally in the "neuroimmunological unit" is equally important in the pathogenesis of Rosacea. Genetic predisposition plus extrinsic or intrinsic triggers (capsaicin, heat, UV light), activates peripheral nerve endings of the skin. Activation of neurons causes vasodilatation, resulting in facial discomfort, which is characterized by pain, redness and burning sensation. The expression of different neuropeptides, Such as pituitary adenylate cycles-activating polypeptide (PACP) or vasoactive intestinal peptide (VIP), substance P and CGRP are enhanced and found to be associated with Rosacea(29). High-affinity neuropeptides receptors on neurotransmitters bind to the arteries or venules to cause vasodilatation (flushing, erythema) or cause plasma extravasations (edema). Activation of T- cells, macrophages, and mast cells by neuropeptides results in activation or aggravation of inflammatory response. It is unknown to what extent neutromediators can exert anti-inflammatory action in human skin diseases. However, the communication between the innate immune and nervous systems exacerbate early Rosacea and lead to chronic disease. Injection with PACAP, a neuropeptides responsible for flushing and edema in human skin up-regulates the expression of the MMP-1, and MMP-9, which can further influence the pathways responsible for cleaving pro-cathelicidin into LL-37 and amplify the inflammatory response(30, 31). PACAP injection also increased the expression of pro-inflammatory cytokines i.e. TNF and CXCL2. These peptides mediate vasodilatation and postulated as critical mediators in the pathogenesis of Rosacea by promoting inflammation and tissue damage(32). Thus dysfunction of neuro-immunology unit may contribute to characterized but transient flushing.

CONCLUSION

The etiology of Rosacea is appeared to be multifactorial genetics also plays a role in the development of Rosacea. In a twin study approach, 50% of the skin findings in Rosacea are accounted for by genetics and 50% accounts by environmental factors. Some triggering factors such as extremes of temperature microbial agents, stress, abnormal vasomotor response to stimuli and chronic solar damage are involved in the development of Rosacea. Besides, TLR-2, KLK-5 and cathelicidin dysfunction or the response of Vitamin-D to skin disease may affect the innate immunity and the appearance of the inflammatory cascade in Rosacea. TH1 and TH17 immune cells also affect adaptive immunity in patients with Rosacea. Moreover, changes in vascular and neurocutaneous structures result in inflammation, vasodilatation, and angiogenesis and conjointly involved in the pathogenesis of Rosacea. In summary, further studies needed to verify their pathophysiology. However, this review might provide a bridge towards more targeted and individualized treatment options for patients with Rosacea.

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