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RESEARCH ARTICLE

THE SKIN BARRIER FUNCTION AND THE DEVELOPMENT OF DERMATITIS.

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Abstract

The skin barrier is a very important element of the body as it plays crucial roles in the immune surveillance and epidermal homeostasis, and in stopping entrance of microorganisms and allergens. The capacity of the skin to protect the body relies on its structure that includes different layers of cells containing components such as proteins and lipids organized in such a way that they provide a tight and strong structure to the skin. Due to various factors, impairments of the structural integrity of the skin occur and compromise its barrier functions provoking thereby immune responses that lead to inflammatory reactions responsible for skin diseases such as dermatitis. According to the causative agent, the location and the symptoms, different types of dermatitis can be identified. These include for example allergic contact dermatitis, atopic dermatitis known as eczema, seborrheic dermatitis and nummular dermatitis. Common symptoms are associated with dry and itchy skin accompanied by the occurrence of blisters. Both genetics and environmental factors play a role in the occurrence of dermatitis. The genetic factors include mutations in genes coding for important skin proteins such as filaggrin responsible for different functions mainly in relation to water retention. Environmental factors can be associated with allergens, detergent, surfactant, excessive washing and exfoliation, and inappropriate diet.

This research paper provides an overview of the occurrence of dermatitis in relation to defects in the skin barrier function. Different types of dermatitis, the normal skin structure components, and its associated functions are discussed. Moreover, the basis for structural defects in the skin in relation to mainly atopic dermatitis, with an emphasis on filaggrin and its genetic underpinnings are reviewed. Aspects of the innate and adaptive immunity, including the role of antimicrobial peptides and proteases are also depicted.

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Introduction:-

Dermatitis refers to a group of diseases that involved mainly skin inflammation. It can be caused by different factors and occurs in numerous forms. Based on the general definition it can be easily assumed that almost any rash such as psoriasis, skin cancer, and seborrhea is dermatitis, but not all rashes are referred to as dermatitis. The manifestations of the condition are variable according to the type of skin inflammation, but in the majority of individuals, the early

stages of the affection are characterized by red, dry, and itchy skin (WebMD, 2018). Serious forms of dermatitis may generate crusty scales, painful cracks, or blisters accompanied with fluid secretion. The symptoms of dermatitis vary from mild to severe and will look different depending on the section of the body that is affected. Moreover, all people suffering from a form of dermatitis do not endure all symptoms. Dermatitis is common and not contagious in general, but it can make people feel uncomfortable and self-conscious. Certain types of dermatitis can persist for a long time, whereas others may worsen suddenly, depending on the season, exposures, or stress. Some types are more common in children, and others occur more in adults.

The causes are variable and include e.g. health conditions, allergies, genetic factors, and irritants (Thomsen, 2014; WebMD, 2018). These can provoke impairments in the normal function of the skin and immunologic phenomena that result in the inflammation of the skin (Agrawal and Woodfolk, 2014). Various risk factors are also associated with the occurrence of dermatitis. These include factors such as age, allergies and asthma, the specific professional occupation and some health conditions. In fact, dermatitis can occur at any age but some types such as atopic dermatitis start in general in childhood. Individuals who possess a family history of e.g. some forms of dermatitis, hay fever or asthma are more prone to developing the condition. Also, some jobs involving contact with specific elements such as metals, solvents or cleaning materials enhance the risk of occurrence of particular inflammations such as contact dermatitis. Medical staff exposed to many adverse conditions can easily develop hand eczema. Other people at risk are those suffering from some diseases or disorders, for instance, congestive heart failure, Parkinson's disease and HIV (Mayo Clinic, 2018).

With regards to diagnosis, dermatitis is usually detected clinically according to the history and appearance of the inflammation (Thomsen, 2014; WebMD, 2017). It is possible to differentiate the various types of dermatitis, but sometimes discriminating the numerous forms of the condition is a fastidious task. Some tests can help with the identification including e.g. skin tests for contact or atopic dermatitis or a KOH test that helps identify a fungal infection (Thomsen, 2014; Mayo Clinic, 2018). Bacterial infection can also be detected in the fluid secreted in blisters.

There are combinations of self-care procedure and medications that can support an effective treatment of dermatitis. The treatment and/or alleviation of the symptoms are more efficient when the type is clearly identified. One measure that can help is the frequent moisturization of the skin. In fact, a lack of moisture results in a dry skin which in turn causes cracks in the epidermis (the outer layer of skin) responsible for an inhibition of the skin barrier function. The use of topical medications or antihistamines can help reduce itching and scratching. It is also important to avoid the usage of substances such as perfumes or harsh detergents that have irritating and drying effects. Although not always necessarily related, fungal infections can support the occurrence of dermatitis and need to be treated as soon they are detected to avoid detrimental impact on the skin (Thomsen, 2014; Mayo Clinic, 2018; WebMD, 2018).

The epidemiology of dermatitis is variable according to the type and the geographical location. For atopic dermatitis, for example, population-based investigations in the USA have provided an estimation of the prevalence of over 10% in both children and adults (Silverberg and Hanifin, 2013). For the specific case of 5-9-year-old children, a prevalence of 17.2% was demonstrated (Spergel, 2010; Hogan et al., 2012). Usually, the disease starts in childhood and can either resolve spontaneously (in the majority of the cases) or progress into adulthood and create debilitating situations in the individuals. In Japan, it is suggested that the prevalence for atopic dermatitis in children may be as high as 11-25% whereas in New Zealand a prevalence of 15.8% in 3-5-year-old children was reported (Purvis et al., 2005; Hogan et al., 2012).

The general objective of the current manuscript is to review the physiopathology of dermatitis especially in the relation to impairments in the skin barrier function that are responsible for the occurrence of dermatitis. An overview of different types of dermatitis and the structure and normal function of the skin will be first depicted to allow a better understanding of the disease and the elements of the skin barrier that may be involved in dermatitis. Different forms of the skin barrier functions will be discussed, especially in relation to the particular type of atopic dermatitis also known as eczema.

Different types of dermatitis:-

According to the causative element, the location and the symptoms, different types of dermatitis can be identified (Mayo Clinic, 2018; WebMD, 2018). These include:

Allergic contact dermatitis:-

this type of dermatitis is a skin allergy which occurs after direct contact, even if only briefly with some irritants or allergens including e.g. poison ivy, nickel-made jewelry, cleaning compounds, perfumes, cosmetics, and preservatives added in many creams and lotions. Some flowers, herbs, fruits, and vegetables can cause allergic contact dermatitis. It is a form of hypersensitivity reaction associated with allergens and antibodies and typically results in a pink or red itchy rash.

Irritant contact dermatitis: this form occurs as a result of an exposure to irritating chemicals or detergents. Repetitive contact with harsh compounds aggravates the skin. The most usual manifestations are dry and damaged skin caused by e.g. over-washing of the hands. In the latter case, the irritant is the water and/or the washing soap that is drying out and damaging the skin with repeated exposure.

Atopic dermatitis:-

It is also called eczema and is one of the most common and studied skin inflammations. It is caused by a combination of factors such as dry skin, gene mutations, a dysfunction of the immune system, the presence of microorganisms such as bacteria and yeast on the skin and environmental conditions. It is a generally a family-related affection which is often associated with allergies, hay fever, asthma, stress, and very dry skin. Impairments in the skin barrier structure and function resulting in a release of moisture and potential penetrations of infectious germs may play an important role in the occurrence of the disease. Atopic dermatitis is an allergic-type reaction and is associated with different manifestations which cause the skin to itch, scale, swell, and sometimes blister. Most patients, including those with the most severe type of the illness exhibit high levels of total IgE in the blood serum. Moreover, they are very sensitive to numerous allergens from diverse sources, and skin-colonizing microbes.

Seborrheic dermatitis:-

It is also known as cradle cap in infant and occurs in the form of yellow, greasy scales like dandruff on the scalp and hair-bearing areas of the face (e.g. eyebrows, or along the sides of the nose), the neck, upper torso and also the genitals. This type of dermatitis condition may be caused by a yeast (fungus), a germ that can be found in the oil secretion on the skin. The condition seems to be seasonal as it can appear and disappear at particular seasons of the year. It can be worsened by stress. When occurring on the scalp of adult seborrheic dermatitis is considered as dandruff and is associated with intense itching.

Nummular dermatitis:-

It can occur at any place on the body as coin-shaped patches and is related to dry skin. Most common body sections where it is often seen include the legs, hands, arms, and chest. It occurs most commonly in the late adulthood stage with the peak age of onset being between 55 and 65. It is more common in men than in women. Dry environment or frequent very hot showers can trigger nummular dermatitis.

Stasis dermatitis:-

This type is usually located on the ankles and lower legs of people suffering from venous insufficiency, varicose veins, congestive heart failure, or other conditions that cause chronic leg swelling. In this case, poor blood circulation in the legs results in a poor blood return creating thereby a blood pooling and fluid buildup and swelling. The swelling causes the skin irritation, especially in the area of the ankles.

Other types of dermatitis:-

These include inflammations such as diaper dermatitis, a kind of irritant dermatitis that is triggered by prolonged exposure of the skin to wet diapers, dyshidrotic dermatitis also known as pompholyx which occurs usually on the hands or feet and is characterized by redness, scaling, and deep blisters, auto-sensitization dermatitis, an itchy rash that constitutes a reaction of the body to intense inflammatory process due to a fungal infection mainly, and lichen simplex chronicus caused by a prolonged scratching of an area of the body that causes the skin to thicken.

Skin barrier dysfunction and associated skin inflammations: case of atopic dermatitis:-**Structure of the skin:-**

The skin is formed by different layers that are made of various compounds such as lipids and proteins (Thawer-Esmail, 2011). There are three different main layers including the epidermis, dermis and subcutis. The epidermis is responsible for the barrier function of the skin and is composed of four layers: the stratum corneum (SC) which constitutes the outermost interface between the air and the body, the stratum granulosum, the stratum spinulosa

situated between the stratum granulosum and the fourth layer called basal layer (Figure1) (Thawer-Esmail, 2011; Hogan et al., 2013). The epidermis is located at the dermal interface and reposes on the basal membrane which is a semipermeable structure. The different layers of the epidermis have different functions that they can achieve due to their composition in specific structured cells known as keratinocytes (KCs). Cell division occurs constantly in the basal layer. The production of the proteins and lipids needed for construction of the barrier function is operated in the spinous layer. Once synthesized, the lipid and hydrolysing enzymes are accumulated and organised into organelles designated as lamellar bodies and are later released in the upper granular layer by exocytosis. In the granular layer, an important protein named filaggrin (filament aggregating protein) produced from profilaggrin (a precursor protein) during the terminal differentiation of epidermal cells is kept in keratohyaline granules and released. The protein plays a crucial role in the regulation of epidermal homeostasis and the skin barrier function especially in relation to water retention. In the spinous layer, the presence of intermediate filaments provides the structural support for the cells. They attach to specialised cell connections called desmosomes that link the cell together generating a microscopic spinous appearance. The fatty compounds including free fatty acids, ceramides and cholesterol and the proteins constituted by filaggrin, involucrin, loricin, and transglutaminase enzymes are secreted in the upper granular layer from the organelles. They interact to generate the corneal envelope, through various procedures involving discriminatory apoptosis (programmed cell death), aggregation of keratin filaments, and crosslinking of proteins with lipid molecules (Thawer-Esmail, 2011).

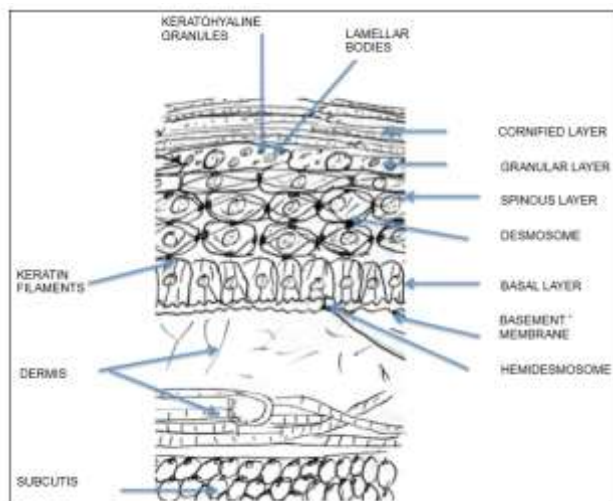


Figure 1:- the structure of the skin (Thawer-Esmail, 2011)

Normal function of the skin barrier:-

The skin is responsible for many metabolic functions of the body. With regards to its barrier function, a simple explanation would be that the skin insures an appropriate water retention in the body, facilitate the excretion of unwanted substances and prevent the entrance of potential harmful compounds and germs. It constitutes a barrier between the body and the external world and can be compared to a brick wall that surrounds a house. As mentioned above the main role of the skin is to prevent excess water loss and keep the body well hydrated. Water plays an important part in the physiological activities occurring within the skin such as various enzymatic processes in relation to exfoliation and the regulation of the skin cell turnover. The other crucial barrier role of the skin is to prevent as much as possible the entrance of bacteria, toxins and allergens into the body, providing thereby a protection against diseases. The barrier function of the skin can be divided into three parts including a physical, chemical and immunological function (Thawer-Esmail, 2011).

The physical barrier function:-

It mainly relies on the stratum corneum, the outermost layer of the skin formed of multiple stacks of corneocytes which are specialized flattened cells of keratinocytes (Proksch, Brandner, and Jensen, 2008; Thawer-Esmail, 2011). These anucleated cells are rich in proteins and are each coated with a thick water-repellent layer of fat acting like a cement or glue to allow the cells to hold together and form a structure known as the extracellular matrix. The stratum corneum constitutes the principal barrier against the percutaneous penetration of microbes and other unwanted compounds. There are also nucleated cells that contribute to the physical barrier by tightening and filling

gaps in the junctions with their cytoskeleton. Such structures within the stratum corneum provide a physical barrier protection by averting water loss and penetration of germs, allergens and irritants. Moreover, they provide mechanical support of the skin.

The chemical barrier function:-

It is ensured by various components. These include lipids and several acids including free fatty acids, lactic acid generated from sweat excretion and urocanic acid from the degradation of the filaggrin protein (Benedetto et al., 2009). Also, antimicrobial peptides namely the human beta defensins (HBD) and cathelicidins which are produced by keratinocytes lamellar bodies and the filaggrin protein that aggregates keratin filaments and produces natural moisturising substances play crucial roles. All precited substances work collectively to ensure important functions such as keratinisation and lipid synthesis. Furthermore, they ensure protection against microbes and an appropriate hydration of the skin (Thawer-Esmail, 2011).

Immunological barrier function:-

This is related to the innate immune system mainly and involves the physical barrier, cells, secretory elements such as antimicrobial peptides and cytokines (Cork, 2009). It also code for specific proteins known as pattern recognition receptors (PRR). Various cells are involved in the immunological barrier function including keratinocytes as well as dendritic, Langerhans, neutrophils and natural killer cells.⁴ The antimicrobial peptides (AMP) like cathelicidin LL-37 originate from the keratinocytes and their production is triggered by an inflammation or injury (Benedetto et al., 2009). There is an exception with the type D1 of human beta defensins which is always present in the keratinocytes. Antimicrobial peptides are compounds capable of elimination a wide range of microorganisms including bacteria, fungi and some viruses. Type D2 and D3 of human beta defensins as well cathelicidin LL-37 have been reported to possess efficient activities against staphylococcal species. Viruses like the Herpes simplex virus-1, virus-2 and the Vaccinia virus are also potentially eliminated by LL-37 (Benedetto et al., 2009). Mechanisms by which the keratinocytes cells recognize the presence of germs involve elements such as transmembrane and intracellular PRR including toll-like receptors (TLR). In the immunological barrier function, cell proliferation and lipid synthesis are activated by cytokines like tumour necrosis factor alpha (TNF- α), interleukins (IL-6 and IL-1 α) which are produced by the innate immune system cells. Cytokines play a crucial role in skin barrier repair. Their expression is enhanced by a barrier disruption. However, when the disruption is prolonged there is an excessive secretion of cytokines which causes an inflammation and epidermal proliferation. To some extent, the immunological barrier function involves an adaptive immune response which involves cells that interact with lymph nodes via the skin lymphatics and trigger a response (Thawer-Esmail, 2011). There is also the implication of antigen presenting cells such as the Langerhans cells, dermal dendritic cells and KCs and T lymphocytes that perform immune response by interacting with endothelial cells. The immune response to an antigen varies according to the type of the antigen which then instruct the T cells to produce T-helper (Th)1 or Th2 cytokines (Cork, 2009; Thawer-Esmail, 2011).

Skin barrier function impairments:-

As mentioned earlier in the manuscript, the skin barrier can be compared to a brick wall that surrounds a property. The brick can be assimilated to the skin cells (keratinocytes) and the cement that glue the brick together as the lipids coating (Elias and Williams, 2015). It is well known that a wall made of bricks are strong and long lasting as long as a serious mechanical or manual destroying forces are not applied to it. However, if this is the case, for example if the cement between the bricks are suddenly or gradually removed, the wall will weaken and eventually fall apart (Elias and Williams, 2015). This scenario can be applied to the skin barrier if it gets compromised. The outcomes can be detrimental to the health of skin first then that of the whole body. One obvious consequence of a compromised skin barrier is an increased trans-epidermal water loss leading to skin dehydration and eventually dryness (Cork, 2009; Elias and Williams, 2015). Moreover, the compromised barrier will not be able to prevent bacteria and allergens to enter the skin and trigger an autoimmune response. Thus, inflammation causing diseases such as acne, rosacea, dermatitis and psoriasis are likely to occur. Therefore, it is important to treat skin impairments as soon as they are detected, to allow a quick repair of the system and avoid more serious health issues.

Genetic elements involved in skin barrier dysfunction leading to atopic:-

Dermatitis in atopic dermatitis, many genes are involved in the occurrence of the disease and can be transmitted to further generations (Cork et al., 2009; Thawer-Esmail, 2011; Leung, 2013; Agrawal, R. and Woodfolk, 2014). It is the reason why the condition is referred to a family related illness. Specific genes involved in the pathophysiology of the atopic dermatitis are those that particularly code for epidermal structural proteins and those coding for important elements of the immune system (Cork et al., 2009). With regards to the structural proteins, the gene encoding the

production filaggrin is the strongest known genetic risk factor related to the occurrence of atopic dermatitis (Cork et al., 2009; Thawer-Esmail, 2011; Agrawal, R. and Woodfolk, 2014). It has been reported that there is strong association between atopic dermatitis and mutations appearance in the filaggrin protein gene which are located on a chromosome 1 (Palmer et al., 2006). It is estimated that about 10% of individuals from the western populations possesses mutations in the filaggrin gene, whereas about 50% of all patients suffering of atopic dermatitis exhibit such mutations (Thomsen, 2014). The occurrence of mutations in the filaggrin gene increase the appearance of functional impairments in the filaggrin protein leading to a disruption of the skin barrier. Cork et al. (2009) reported that 17 and 20 mutations in the filaggrin genes have been detected within European and Asian populations respectively. The mutations result in a clinical expression of dry skin flanked with many fissures that lead to a higher risk of development of atopic dermatitis. This can be explained by the fact that the mutations cause a reduced ability of the corneocytes to keep water due the decreased concentration of humectants and a defective cornified envelope of the corneocytes, which also impact negatively on the elasticity of the skin and its mechanical resistance (Cork et al., 2009). Such types of barrier impairments are anticipated to enhance the risk of entrance of irritants and allergens in the skin due to potential occurrence of gaps between the shrunken corneocytes. Although, mutations in filaggrin protein are responsible for dermatitis, not all individual with the conditions possess these mutations. Other genetic factors such as intragenic copy number variation within the filaggrin gene have been shown to sustain the risk of atopic dermatitis with a dose-dependent impact (Irvine, McLean and Leung, 2011). Also, mutations in other genes such the SPINK5 and CSTA genes encoding protease inhibitors have been reported to cause barrier function defects that activate the occurrence of atopic dermatitis (Cork et al., 2009). Moreover, the condition commonly occurs as a result of the combination of genetic variants and environmental and developmental risk factors.

Environmental elements involved in skin barrier dysfunction leading to atopic dermatitis:-

Defects in the skin barriers are commonly relates to a long period of repeated aggressions and accumulative irritation on the skin. These literally destroy the extracellular matrix and the lipids coating that holds the cells together resulting in an overly sensitised skin (Millward, 2018). Such aggressions include a variety of practices and substances usages such as over-cleansing with hard water, soap and detergents, over-exfoliation the skin, hostile skin treatments, insufficient protection against free radical resulting in UV related damage, exposure to long-term emotional stress and conducting low fat diets leading to essential fatty acid deficiency. With regards to misuse use of certain substances, it is worth mentioning the usage of skincare products with the inappropriate pH or strong surfactant characteristics and topical moisturisers that is composed of known irritants (such as SLS, PEG's, synthetic fragrance and colours). Over usage of compounds such as Alpha Hydroxy acids and retinol can be detrimental to the skin as well as exposure to house dust mites and food allergens (Cork, 2009; Millward, 2018).

Using soap and detergent especially in an inappropriate way is one of the main cause of occurrence of contact dermatitis and also atopic dermatitis (Cork et al;2009). The reason is that those compounds work by emulsifying the foreign and natural fats located on the skin which can then be drained off with water. Excessive usage such products is ineluctably detrimental especially if after washing, the skin is not treated with a good restoring cream. This leads to negative effects such as scaling, dryness, tightness and roughness, erythema, and swelling (Ananthapadmanabhan et al., 2004; Cork, 2009). It is proposed that the precited impairments of the skin is due to an increase of trans-epidermal water loss as a result of the solubilization of the epidermal lipids (Cowley and Farr, 1992). In individuals suffering from atopic dermatitis, a significant increase in trans-epidermal water loss is observed in comparison with healthy people. This can be screened by performing a standard test for susceptibility to irritation using the detergent sodium lauryl sulfate. It has been suggested that severe irritant effects of soap and detergents are partially associated with the secretion of pro-inflammatory cytokines from corneocytes (Cork, 2009). Moreover, the impact of the irritant compounds on the pH of the skin constitute a serious triggering factor of the epidermal barrier function ailments (Leung, 2013).

With regards to the implication of house dust mites in the occurrence of dermatitis, it has been suggested that this is associated with the presence of over 30 different proteins in the mites that can activate IgE-mediated responses such as those involving cysteine and serine proteases (Nemoto-Hasebe et al., 2009). Studies have shown that these proteins degrade adhesion proteins and enhance the permeability of the lung epithelium (Winton et al., 1998). It can then be suggested that the same effect may occurs at the skin barrier level. In fact, patch tests performed on the skin demonstrated that two dust mite proteins namely Der p1 and Der p2 possess proteolytic activity that can provoke irritative or immune reactions and this was not necessarily associated with increased levels of levels of IgE (Deleuran et al., 1998). The inflammatory power of such proteins is then linked to their proteolytic activity or their capacity to trigger IgE-mediated responses or both. Studies have also demonstrated that house dust mite that

possess a capacity to degrade proteins as well as allergens from cockroach can stimulate a barrier disruption and activate PAR2 (ref). As a result, the penetration potential of allergens and microorganisms is intensified leading to potential skin barrier dysfunctions and occurrence of skin disorders. Although the increase of the level of IgE associated with house dust mite allergens can cause atopic dermatitis, it has been suggested that a predisposition to a defective barrier condition is required for an effective effect of such IgE (Nemoto-Hasebe et al., 2009; Cork, 2009).

Conclusion:-

Dermatitis occurs as a result of impairments of various skin (mainly the epidermis) components leading to a barrier dysfunction at physical, chemical and immunological levels. In general, an interplay between genes and the environment support the occurrence of dermatitis. In fact, genetic mutations in people with atopic dermatitis impact negatively their skin barrier function. Moreover, risk factors related to the environment stimulate immune responses that result in inflammatory reactions which can adversely impair skin barrier function in atopic dermatitis. Clinically speaking, the defects result in manifestations such serious pruritic, inflamed skin that become more prone to the penetration of irritants and allergens and predispose individuals to colonization and infection by microbes.

Dermatitis can be managed by different procedures and treatments. When the diagnosis is confirmed, it is advisable to avoid as soon as possible the environmental triggers such as perfumes and harsh detergents. In patients with heterozygous gene mutations treatment aiming at the barrier maintenance/restoration can help manage at an early stage the condition. The use of topical medications or antihistamines can help alleviate symptoms such as itching and scratching. Individuals with family history of dermatitis should be alert about the occurrence of any dryness and itchiness as these symptoms constitute the first sign of barrier disruption. It is recommended that people engaged in jobs involving the manipulation of irritant compounds use appropriate protective equipment.

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