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Boosting the Anti-viral Defense of the Skin

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Boosting the Anti-viral Defense of the Skin

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abstract

The body's immune system recognizes infections with pathogens and reacts towards them in a two-phasic response. In particular, the anti-viral response has caught attention throughout the past year, in which SARS-CoV2 (severe acute respiratory syndrome coronavirus-2) has kept the world in suspense. Training the immune system can have beneficial effects and allows for a faster reaction towards infections, and it was shown that β-glucan promotes trained immunity. CM-Glucan Forte, the water-soluble version of β-glucan combined with magnesium, was previously shown to balance the skin's immune system, alleviating signs of atopic and stressed skin. New data indicate that CM-Glucan Forte is further able to stimulate the anti-viral defense of keratinocytes by upregulating a set of genes that support skin cells' reaction upon infection with a virus and thereby contributing to the anti-viral defense of the skin.

Virus infections and the viral replication cycle

Viruses are submicroscopic infectious organic structures which exploit eukaryotic cells to amplify themselves and spread. For this, it is important to understand that the replication of a virus is not possible without a host cell which provides the machinery for multiplication of the virus genome and synthesis of the structural proteins that make up the virus envelope and capsid. In this way, the virus goes through a replication cycle every time a host cell is infected.

This cycle consists of several steps:

- **Viral entry:** Through specific interaction of a protein on the surface of the virus with a protein (often a receptor) on the surface of the host cell, the virus can attach to the cell surface. The virus is subsequently taken up by the host cell and its genome is released.

- **Replication:** On the one hand, the viral genome is multiplicated by DNA or RNA polymerases (depending on the type of virus) and on the other hand, it is transcribed to mRNA which codes for the proteins making up the virus. These are then produced by the cellular ribosomes.

- **Assembly:** Once all of the viral proteins as well as copies of the viral genome are available, viral particles are assembled within the cell.

- **Release:** The fully assembled viral particles are released into the extracellular fluid, while the infected cell continues to produce new viruses.

The cellular anti-viral defense

The immune system is the body's protection system from infections with bacteria, viruses and foreign bodies that could harm the body. It consists of two parts that work closely together: the innate (general) immune system and the adaptive (specialized) immune system. The innate immune system is often the body's first line of defense and reacts quickly, but non-specifically, towards pathogens that enter the body. However, it has limited power in preventing the spread of viruses or bacteria and therefore activates the adaptive immune system for further support. The role of the adaptive immunity is the targeted elimination of the pathogen by recognizing the type of germ that causes the infection and specifically attacking it through production of neutralizing antibodies and cytotoxic T-cells that eliminate bacteria or cells infected with a virus. While this is usually a slower process due to the need to first identify the pathogen, it offers the advantage of forming an immune memory which allows for a faster reaction the next time the body encounters the same pathogen.

As part of the innate immune system, most cells of the body are able to detect viruses both at their cell membrane and in the cytoplasm though recognition of viral nucleic acids and proteins by so-called pattern recognition receptors (PRR). Binding of viral DNA or RNA to specific PRRs triggers a signaling cascade which results in the secretion of signaling molecules known as inflammatory cytokines and interferons, which attract immune cells that help to fight off the infection and warn neighboring cells of the threat of a potential viral infection, respectively. In response to interferons, surrounding cells upregulate the expression of interferon-stimulated genes (ISGs), a large group of genes which help the

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cells to prepare for a viral infection. The protein products of these genes control virtually all steps of the viral replication cycle, for example through blocking the attachment and entry of the virus into the cell, by preventing the import of viral nucleic acids into the host cell nucleus, by inhibiting synthesis of viral proteins or through preventing the assembly and release of the viral particles [1].

In addition to increasing the antiviral defense locally, cytokines and interferons also attract immune cells to the site of infection. These recruited immune cells help to clear infected cells and amplify the immune response by involving the adaptive immune system. For this, specific cells, broadly termed antigen presenting cells (APCs), process the virus in order to subsequently present parts of it on their surface to activate other types of immune cells. Once the APCs have found and activated immune cells that specifically recognize the infecting virus, these start the second phase of the immune response, consisting of antibody production and targeted elimination of infected cells **(Figure 1)**. In this way, circulating viruses can be neutralized and destroyed before infecting further cells, while cells already infected with the virus can be cleared und ultimately tissue repair can be initiated. These mechanisms occur in most tissues of the body, and are particularly important in the skin, which is our first line of defense against all kinds of infections as it is in constant contact with the outside world.

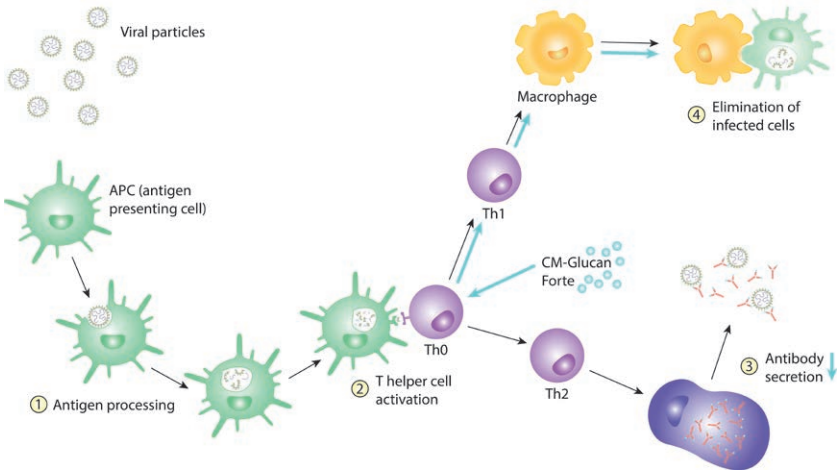

Fig. 1 Immune responses to viral infections.

Very quickly after the beginning of the pandemic, it was shown that on the molecular level, SARS-CoV2 attaches to cells by docking to the angiotensin converting enzyme 2 (ACE2) using the spike protein on its surface, and thereby initiates its uptake into cells **(Figure 2)**. Once inside, the virus uses the cell's replication and protein production machineries to produce new viral particles. When fully assembled, these can exit the host cell and spread within the body or, for example, through sneezing or coughing, to other people.

Despite its actual function in regulating the blood pressure, ACE2, the cell surface receptor for SARS-CoV2, is not only expressed in the cells lining the blood vessels. As the respiratory disease caused by SARS-CoV2 suggests, this molecule is also present on the cells lining the nasal cavities and the lung, and therefore allows the virus to infect these cells [2]. Quite surprisingly, ACE2 is also highly expressed in various other tissues, including the kidney, heart, gastrointestinal tract and the skin [3]. There, it was recently published to be

SARS-CoV2 and the ACE2 Receptor

One specific virus, namely the coronavirus family member SARS-CoV2 (severe acute respiratory syndrome coronavirus-2), has rushed the whole world off its feet for most of the past year. An infection may lead to the severe respiratory disease termed COVID-19 (coronavirus disease 2019) which has caused hundreds of thousands of deaths worldwide until now. Ongoing research is focusing on the development of both vaccines and pharmaceuticals to prevent the spread of the virus and to treat the progression of this serious disease, respectively. Further, the molecular events taking place during viral infection are being studied extensively by researchers all over the world.

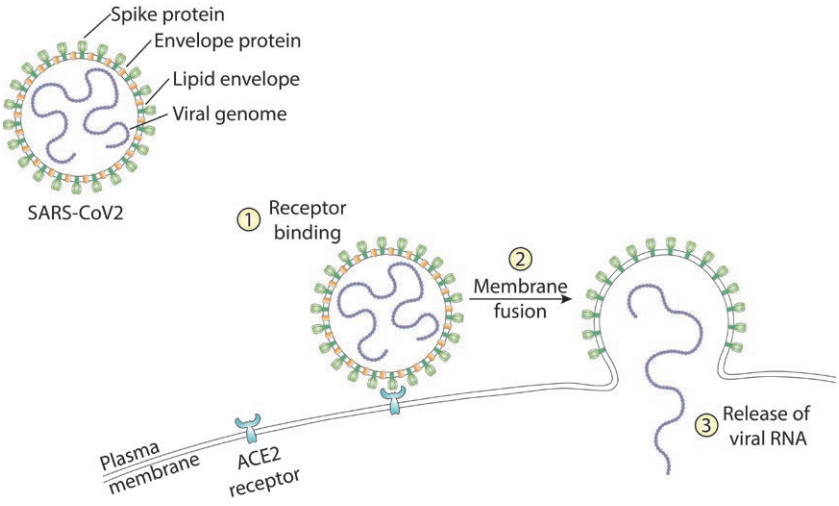

Fig. 2 SARS-CoV2 binding to the ACE2 receptor.

present on keratinocytes, particularly in the basal cell layer of the epidermis, and to be enriched around hair follicles and in cells from sweat and sebaceous glands [4,5]. Further research on the skin as a potential route of entry into the body for SARS-CoV2 would thus be of big interest.

Modulation of the immune response by CM-Glucan Forte

Boosting the antiviral immunity of the skin might be a beneficial strategy, particularly in these times of increased need for protection. This might for example be achieved by topical application of CM-Glucan Forte, a carboxymethylated and thus water-soluble version of β-glucan combined with magnesium. It was shown that β-glucan induces trained immunity, a process which prepares immune cells for an infection by setting them in an alert state and therefore allows them to react faster and stronger when encountering a pathogen [6]. In addition, we have shown that CM-Glucan Forte balances the skin's immune response. Ideally, the activation of a specific type of cells termed T helper (Th) cells by APC initiates the differentiation to both Th1 and Th2 cells that in turn activate a cellular and antibody-mediated immune response, respectively. However, especially in atopic dermatitis, the normally balanced ratio is shifted towards a Th2 response resulting in the production of immunoglobulin E (IgE) antibodies that induce the degranulation of mast cells. This causes the typical symptoms of allergies such as itching and inflammations. In this setting, CM-Glucan Forte acts as a "personal trainer" for the skin and helps it to regain its natural Th1/Th2 balance. It suppresses the allergy related Th2 response and reduces the expression of IgE antibodies which mediate hypersensitivity reactions. By redirecting the immune response to a Th1-mediated reaction, the skin can be additionally supported to react towards viral infections. Therefore, CM-Glucan Forte offers not only relief for already stressed skin, but it additionally supports the skin by preparing it to defend itself from pathogens such as viruses or bacteria.

New insights into the effect of CM-Glucan Forte on anti-viral immune responses

To further investigate whether CM-Glucan Forte can support the immune response in the skin in fighting off potential viral infections by inducing the antiviral response, a study was performed in epidermal keratinocytes obtained from an aged donor. This model was of particular interest as it is known that the anti-viral response is generally impaired in the aged population [7]. For this study, normal human epidermal keratinocytes (NHEK) from a 55-year old donor were incubated with 2 mg/ml CM-Glucan Forte for 48 hours prior to analysis of several ISGs and anti-viral genes.

Treatment with CM-Glucan Forte stimulated the expression of the ISGs ADAP2 (ArfGAP with dual PH domain 2) and GBP1 (Guanylate binding protein 1) by 442% and 202%, respectively. During viral infections, ADAP2 blocks the entry of RNA viruses into the cells, while GBP1 promotes autophagy of viral replication complexes, thereby effectively contributing to clearance of the viral particles from the cytoplasm and helping to prevent the further spread of the virus.

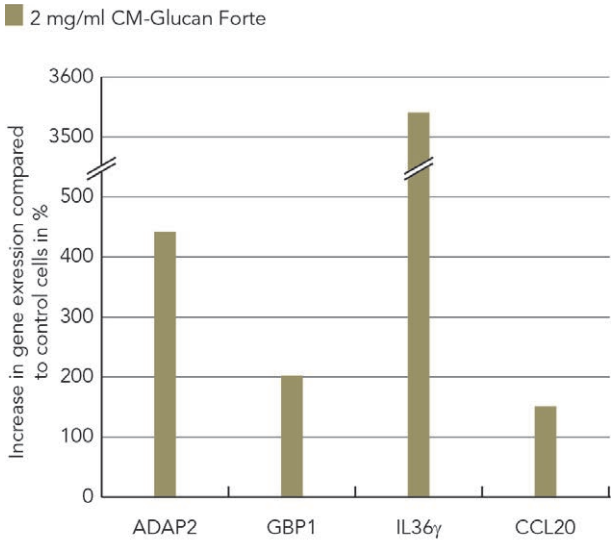

Fig. 3 CM-Glucan Forte upregulates the anti-viral immunity in NHEK.

The expression of IL36γ (Interleukin 36 gamma), an interleukin which participates in the anti-viral response and which counteracts viral immune evasion strategies around the related IL-1, was stimulated by 3541% upon treatment with CM-Glucan Forte. In addition, the chemokine CCL20 (Chemokine (C-C motif) ligand 20), that is involved in the antiviral response by attracting immune cells to the site of infection, was upregulated by 151% upon treatment of NHEK with CM-Glucan Forte. These proteins therefore help the keratinocytes to activate the adaptive immune system for further clearance of a potential viral infection.

Overall, the changes in gene expression of ISG and anti-viral genes indicate that CM-Glucan Forte supports the immune system of the skin by preparing the cells for fending off a viral infection.

Conclusion

Supporting the immune system has become a trend in health care and nutrition. Especially the skin as our first line of defense is exposed to numerous threats from pathogens such as bacteria and viruses. CM-Glucan Forte is able to boost the anti-viral immunity of epidermal keratinocytes, preparing them for a potential viral infection.

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