We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Chapter

Sunlight and Herpes Virus

Vittorio Mazzarello, Marco Ferrari, Stefano Decandia and Maria Alessandra Sotgiu

Abstract

The Herpesviridae are a family of viruses widely spread in nature that can infect a wide variety of species. After the primary infection, the human alphaherpesvirinae sub-family remains quiescent in the nerve ganglia from which it can periodically reactivate, causing clinical manifestations. Although spontaneous recurrences are possible, a wide variety of internal and external triggers may lead to transformation of the Herpes Simplex and Varicella-Zoster Viruses from a dormant to a proliferative state. Sunlight is a potent stimulus for the alphaherpesvirinae reactivation. The purpose of this paper is to analyze various features of this correlation and several steps you can take to lower your risk of triggering a herpes outbreak after sun exposure. Learning how to reduce the recurrence is extremely important and it is necessary: to perform a gradual and progressive sun exposure; to know what garments to wear; to know the environmental conditions of exposure; to know each skin phototype; to use a protective product against UVB and UVA with sun protection factor suitable for each phototype and environmental conditions.

Keywords: sunlight, UV, UVR, herpes virus, HSV, herpes zoster, VZV, sunscreens, prevention

1. Introduction

The sunlight and specifically the Ultraviolet component of its radiation (UVR) is among the major causes of alphaherpesviridae (αHV) reactivation. Various aspects of this correlation will be analyzed in this chapter, as well as how it interferes with the virus-host relationship and what kind of precautions should be taken to reduce the risks of painful relapse.

2. Herpes virus

The Herpes Virus (HV) are a members of the family Herpesviridae widely spread in nature that can infect a wide variety of species of at least two animal phyla, the Chordata and the Mollusca [1]. It is a virus about 150–200 nm in diameter, with icosahedral nucleocapsid DNA double helix containing an envelope which derives from the nuclear membrane of the host cell with viral glycoproteins that protrude on the surface.

To date a total of 8 human HVs are known, having the characteristic of establishing a life-long latent infection: a state from which the virus can be reactivated and result in recurring disease. The HV family is divided into three subfamilies (Alphaherpesvirinae,

Betaherpesvirinae, and Gammaherpesvirinae); among these, only the αHV creates skin lesions in humans [2]. The Herpes Simplex Virus (HSV), creating the general clinical picture of herpetic disease, and the Varicella-Zoster Virus (VZV), which is the cause of chickenpox and Herpes Zoster (HZ), both belong to αHV.

2.1 Clinical aspects of αHV lesions

The transmission of αHV occurs by close contact with a person who actively eliminates the virus. The viral diffusion occurs from lesions; however, it can occur even if they are not visible. After the primary infection, the αHV remains quiescent in the nerve ganglia from which it can periodically reactivate, causing clinical manifestations. The HSV commonly cause a relapsing mucocutaneous infection affecting the skin, mouth, lips, eyes and genitals. Serious common variants include encephalitis, meningitis, neonatal herpes, and infections disseminated in immunosuppressed patients. There are two types of HSV: Herpes Simplex Virus 1 (HSV-1) and Herpes Simplex Virus 2 (HSV-2) and both types can cause oral or genital infections. In most cases, the HSV-1 causes gingivostomatitis, cold sores, herpetic keratitis, and lesions in the upper body. The HSV-2 generally causes lesions to the genitals and to the skin of the lower half of the body. Approximately 70% of population in USA is seropositive for HSV [3] but only the 20%, due to a decline in cellular immunity, presents the recurrent form that can occur with a variable frequency. The mucocutaneous manifestations occur in two forms: primary infection and recurrent infection. Both forms appear on the skin with an erythematous lesion with vesicles (the size of a pin's head) clustered that can merge to form a bubble and then break, leaving an erosion and then a crust that falls after a few days. The primary infection may be unapparent, so that most individuals carry antibodies but have no memory of the initial Herpes. In the forms where the disease manifests itself usually appears in children aged between 6 months and 3 years of age. It presents a clinical presentation often more serious than the classical that is shown in the recurrent form. In fact, it is associated with general malaise with temperature over 39°C, pain, dysphagia, sialorrhea, fetid breath. Despite the impressive appearance it resolves on its own in 10–15 days. During the primary infection the transmission of the virus is favored by alterations of the epithelial lining, so that it penetrates and multiplies in the epithelial cells, with lysis of the infected cells due to the formation of a large number of virions. The virus then disappears from the coating epithelium and goes, passing through the sensory nevi, to localize in the nerve ganglia corresponding to the entry area. In recurrent manifestations usually, after a prodromal period (typically <6 h in HSV-1 relapses) characterized by burning or pruritus, small vesicle bunches appear stretched on an erythematous base. The bunches are 0.5–1.5 cm in size but can flow together. Skin lesions of the nose, ears, eyes, fingers or genitals can be particularly painful. The vesicles normally persist for a few days, then break and dry, forming a thin yellowish crust. The lesions can be associated with a burning sensation, tingling or itching with or without fever and small adenopathies, the evolution lasts 1–2 weeks. The herpetic lesions typically heal completely, but recurrent lesions in the same site can cause atrophy and scarring. Skin lesions can develop bacterial superinfections. In patients with depression of cell-mediated immunity due to Human Immunodeficiency Virus infection (HIV) or other causes, long-lasting or progressive lesions may persist for weeks or longer. Herpes labialis (HL) occurs on the edge of the vermilion of the lip or, less frequently, on the mucosa of the hard palate. HL is the most common clinical form in the facial region [4]. In the United Kingdom it accounts for 1% of medical consultations [5]. The acute gingivostomatitis is characteristic of childhood. Instead, herpetic pharyngitides can occur in adults and children; occasionally, mediated by oro-genital contacts, caused by the HSV-2. The intraoral and gingival

vesicles normally break in a time ranging from a few hours to 1–2 days, leaving an ulcer. Fever and pain often occur; after the resolution, the virus remains quiescent in the semilunar ganglion. The Genital Herpes (HG) is the most widespread sexually transmitted ulcerative disease in developed countries. HG can be caused by HSV-1 or HSV-2. Ocular HSV lesions (HO) can cause corneal scarring, and recurrent ocular HSV infections are a leading cause of vision loss [6]. VZV belongs to the αHV subfamily and produces two clinical syndromes: varicella (chickenpox) and zoster (shingles). Both "zoster" (from Greek) and "shingles" (from French and Latin languages) correspond to the English word "belt," which describes the characteristic narrow, bandlike rash from the spine to the front of the torso on one side of the body [7]. VZV is transmitted by inhalation of respiratory secretions or contact with skin lesions. During the primary infection (varicella), the virus becomes latent in the dorsal ganglia and zoster is due to reactivation from latency, a process which occurs most frequently in elderly [8]. Each person with a history of varicella has approximately a 30% lifetime risk of at least one VZV reactivation [9].

2.2 Pathogenesis

HSV infections are most commonly acquired through direct contact with mucosal tissue or secretions of another infected person and the majority of infections are established within the stratified squamous epithelium of the skin and oral or genital mucosa [10]. The virus is able to cause a lytic infection with direct death of epithelial cells. Following infection, the virus enters sensory nerves that innervate the skin or mucosa and travels via retrograde axonal transport to the neuronal cell body: here it can establish a life-long latent infection in dorsal root ganglia [11]. In the cell body there is the nucleus, where the virus makes use of the cell's apparatus for DNA replication and transcription. The axonal cytoskeleton and molecular motors, like kinesins, are involved in the active transport of viral capsids and glycoproteins: their transport seems to be fast, bidirectional and microtubules dependent [12–14]. The mechanisms that regulate entry into lytic replication versus latent infection in neurons remain largely undefined. The mechanism of HSV entry is mediated by direct interaction between viral envelope glycoproteins and cell surface receptors that mediate attachment, initiate signaling cascades, or trigger virus internalization.

The entry process involves multiple steps:

1. Attachment to the cell surface: the virus initially uses filopodial interaction to migrate toward the cell body and to initiate the access. This process is termed 'viral surfing' [15]. In this process, the initial binding of virus to cells is mediated through association of viral glycoprotein (g)B and/or gC with heparan sulfate proteoglycans (HSPG)s located on the cell surface, facilitating the subsequent binding to coreceptors. The gC makes the first contact with HSPGs on the cell surface, but in the absence of gC, gB can take over this function [16].

2. Binding to cell receptors and coreceptors: the major virus attachment is glycoprotein gD and the most studied coreceptor are nectin-1, herpes virus entry mediator or 3-O-sulfated HS. The interaction of the viral glycoproteins with these cell receptors induces conformational changes recruiting gB, gH, and gL for fusion of the viral envelope with the cell plasma membrane leading to viral penetration and capsid release in the cytoplasm [17]. The link between gD and its receptor can activate the gH/gL complex.

3. Fusion with cellular membrane: gH/gL provides the signal required for activation of gB. Binding of gB to one of its receptors, is required for

delivery of the viral nucleocapsid to the cytoplasm accomplished either by membrane fusion or endocytosis/phagocytosis-like uptake. Beside membrane fusion, mechanisms of endocytosis and/or a phagocytosis-like uptake have been proposed. The endocytosis of HSV particles is atypical, because not mediated by clathrin-coated pits or caveolae. The phagocytosis process requires a cytoskeletal rearrangement with activation of Rho GTPases [18].

After fusion between the cellular membrane with the infecting virus, a viral transactivator tegument protein (VP16), is released into the cytoplasm. The viral capsid is then transported to the nuclear membrane along the microtubule network and, through nuclear pore, the viral DNA is released into the nucleus. VP16 forms a transactivation complex binding in the cytoplasm host cell factor-1 (HCF-1) (protein that contains a nuclear localization sequence), and in the nucleus the homeodomain protein Octamer binding protein-1 (Oct-1). These proteins form a trimeric complex able to activate the immediate early (IE) gene expression [19]. Successful lytic replication is dependent on the expression of the viral IE genes within all infected cells. While this model of VP16 activation of IE gene expression is well understood, the mechanisms implicated in neuronal latency are debated and considerable gaps remain in our knowledge of how different signaling pathways act on the latent genome for reactivation. Following the establishment of latent infection, viral lytic gene expression is silenced, and the lytic gene promoters are associated with repressive heterochromatin [20]. Key experiments performed in the 1980s indicated that latent genomes in the brain stems of infected mice have a nucleosomal structure [21]. Later studies confirmed that the latent viral genome associates with cellular histones in the trigeminal ganglia of mice [22, 23]. Coinciding with the silencing of lytic transcripts, the viral lytic gene promoters become enriched with characteristic heterochromatic histone modifications [24, 25]. While it appears that factors intrinsic to neurons play a key role in the transcriptional silencing of the virus, viral gene products expressed during latent infection can also modulate the chromatin structure [23, 26, 27]. This modulation likely promotes long-term latency, while priming the genome for reactivation following the appropriate stimuli [28, 29].

3. Trigger

Although spontaneous recurrences are possible, a wide variety of internal and external triggers may lead to transformation of the HSV from a dormant to a proliferative state [30].

Some of the following factors may trigger herpes symptoms:

- Sunlight: some study demonstrates UVR as a powerful trigger for HL and it also seems that HZ can be stimulated by sun exposure [8, 31].

- Exposure to heat or cold [5, 32].

- Local tissue trauma may make herpes symptoms appear such as: undergoing a surgery [33], laser surgery [34], dental procedures [35], and Tattoos [36]. Another unusual form of traumatic triggering of HSV reactivation may be neurosurgery: after a delay of approximately 1 week, destructive encephalitis may develop with fever and seizures, and with typical viral inclusion bodies demonstrated by histopathology [37].

- Persistent mental stress and fatigue [33, 38]. Psychological stress can also dysregulate cellular immunity, and enhance latent αHV reactivation [39]. Importantly,

chronically stressed low socioeconomic status individuals have higher antibody titers to latent HV. Additionally, dementia caregivers have greater HSV-1 antibody titers compared with demographically matched controls [40, 41].

- Physical stress: fever[5], illness (infection, septicaemia).

- Nerve damage: minimal stimulation or inapparent trauma to the trigeminal sensory root is sufficient to activate latent HSV in humans [42].

- Radiotherapy: the example of radiation therapy against a brain tumor initiating HSV encephalitis suggests that other trigger factors also should be studied [43].

- Immunosuppression: when the immune system is dysregulated, by HIV or chemotherapy or corticosteroid administration, people generally exhibit greater disease susceptibility and latent HSV or VZV reactivation [43, 44]. Maladaptive alterations in cellular immune function can enhance herpesvirus reactivation and replication, resulting in elevated herpesvirus antibody titers. For instance, organ transplant patients have elevated herpesvirus antibody titers [39, 45–47].

- Sexual intercourse: some people find that the friction of sexual intercourse irritates the skin and brings on symptoms of HG. Even if the friction of intercourse seems to be a trigger for symptoms, it won't probably cause a flare-up every time [5].

- Hormonal changes, like those that occur in the menstrual cycle, can affect herpes outbreaks. There is a significant association of development of recurrence HSV and the luteal phase of the menstrual cycle [5].

- Change in antiviral activity of the saliva [5].

Whether a common pathway exists for pathogenetic processes induced by these disparate reactivating factors remains to be determined.

4. The Sun radiation and interaction whit skin

The skin is continually subjected to the action of external agents including solar radiation. One of the scientifically documented triggers for herpes outbreaks is the ultraviolet (UV) light found in direct sunlight.

4.1 The Sun as origin of the electromagnetic energy

The Sun is a G-type main-sequence star and is the largest and the most massive object in the solar system. The Sun is the source of the overwhelming majority of light, heat, and energy on Earth's surface, and is powered by nuclear fusion of hydrogen nuclei into helium. As a result of these nuclear reactions a continuous flow of particles and electromagnetic waves called the solar wind is released in the cosmos. Solar wind is a constant stream of plasma and particles emanating from the sun and is the extension of solar corona into interplanetary space. The solar wind invests all the planets, can reach speeds above 700 km/s and have a density that varies from 10 to 100 particles/cm^3. Sunlight consists mostly of short wavelength ionizing radiation (cosmic, gamma, and X-rays) and long wavelength non-ionizing radiation (UV, visible, and infrared) [48].

UVR is the area of the electromagnetic spectrum that is considered biologically the most active and therefore of greatest impact on health and disease [49]. For convenience, we separate UV somewhat arbitrarily into UVA (315–400 nm), UVB (280–315 nm) and UVC (100–280 nm). UVC together with ionizing radiation is largely absorbed by the upper atmosphere and does not reach us on the earth's surface. Most UVR that reaches the earth's surface is UVA (95%), only a small percentage is UVB (approximately 5%). UVR peaks around noon and is increased by reflection from snow, water, and sand [50]. UVA, but not UVB, can penetrate glass [51]. The solar radiation is omnipresent during daylight hours. At ground level the amount of UV mainly comprises UVA, and a small percentage (<10%, variable by time of day, season and altitude) of UVB. The doses of UV absorbed vary greatly within a person and between people, depending on the position, time of day, season, type of clothing, habits and skin pigmentation.

The non-ionizing radiation are not lethal to living organisms but can cause damage to the skin and eyes if taken chronically and/or in large quantities. Animals defend themselves from the action of these waves thanks to the presence on their skin of hairs, feathers and scales. Humans, having lost the hair during evolution, have to use melanin as a means of protection. The peculiarity of the UV is that they are one of the few environmental factors that can cause both disease and protection against the disease [52]. The sun exposure is pleasant for us because it causes the following positive effects: we are pervaded by a pleasant feeling of warmth and well-being linked to Infrared Radiation (IR) and Visible Light (VL), we release chemical factors that act as antidepressants (VL), appears after a few hours a dark and transient tanning (UVA), followed by a golden and lasting tan (UVB) after 24–48 h. Other positive actions are the production of "antirachitic" vitamin D (UVB) and a regulation of hormonal functions (VL). Unsuitable exposure can lead to immediate or delayed side effects. The most frequent damages caused by sunlight are: sunburn, photoallergic reactions, photo-aging, skin tumors, eye diseases and immunosuppression.

4.2 UVR and immune skin suppression

Exposure to UVR has a profound effect on the skin immune system. It has both, pro-inflammatory as well as immunosuppressive effects and it involves both innate and adaptive immunity. Examples of pro-inflammatory responses clinically observed include sunburn, photodermatosis [53]. Examples of the immunosuppressive effect is the use of UV for psoriasis or lichen planus treatment. Both UVB and UVA wavebands contribute to sunlight-induced immunosuppression, although an interaction between them makes sunlight more suppressive than each waveband alone. It is therefore important to protect the skin from both UVB and UVA. Exposure to doses of UVR that are only 30–50% as high as what is required to cause barely detectable sunburn, suppressing immunity in humans. Therefore, normal daily outdoor activities during spring and summer months are likely to cause some degree of immunosuppression in a large proportion of humans [54]. It is both obvious and striking that UVR at rather low doses suppresses an immune response. Thus, one may speculate that a certain degree of immunosuppression may be beneficial. The skin is an organ which is constantly exposed to potential allergens; in addition, the skin is an organ which is prone to autoimmunity [55, 56]. Hence, it is tempting to speculate that a certain degree of constant immunosuppression by daily solar exposure may prevent the induction of these immune responses. Owing to the multiple different experimental systems suppressed by UV and the dependence on dose, timing, waveband and skin site, we currently do not have a comprehensive understanding of how UV has this potent effect on the immune system. However, many different molecular and cellular events have been described. The cells involved in immunosuppressive activity are

keratinocytes, lymphocytes, Langerhans cells (LC), macrophages and mast cells. UVR induced immune suppression is known be mediated through T cells [57]. The relation of immune suppression is linked to various subtypes of regulatory immune cells such as regulatory T cells (Tregs) and regulatory B cells (Bregs) depends on UVR doses and type of immune response [58–61]. Furthermore, UVR has also profound effects on antigen-presenting cells. It damages LCs, so that they migrate from epidermis into the draining lymph nodes [62, 63]. It affects mast cells which are known to be involved in immune suppression [64]. It releases cytokines leading suppressor macrophages to infiltrate the skin and activating B lymphocytes in draining lymph nodes so that they have suppressor function. It is likely that interaction between these UV-altered antigen-presenting cells result in the activation of suppressor T lymphocytes. There is good evidence that these T suppressor cells are mainly responsible for reduction in immunity caused by UV [54]. The molecular mechanisms responsible for disruption of cellular immunity and some of the key events observed in the skin after the UVR exposure are described below (**Figure 1**). The cellular-molecular phenomena occur in successive steps. In the first step, which concerns keratinocytes, LC, urocanic acid (UCA) and corneum lipids, some ray-sensitive photoreceptors absorb photons, with different susceptibility for the different wavelengths (so the results can be different depending on the type of UV) and initiate a molecular cascade that damages and modifies the cellular biochemistry. The molecular mechanisms responsible for disruption of cellular immunity begins with DNA damage, trans to cis isomerization of UCA, and peroxidation of lipids. In the second step, the cells damaged by UVR produce mediators (especially cytokines) that modify the activity of LC. In fact, both for the cytokines and for their own damaged DNA, in addition to the alteration of the antigen presentation, they migrate into the lymph nodes. The cytokines produced in this phase are numerous. It has also been observed that UVR suppresses HSV antigen presentation in epidermal cells and leads to the reduction of type 1 cytokine release, an important key-factor in immunological control for viruses such as HSV [65, 66]. Photoproducts of DNA such as pyrimidine dimers or 6-4-photoproducts result in the production and release of various immunosuppressive factors such as Tumor Necrosis Factor (TNF)-alpha and

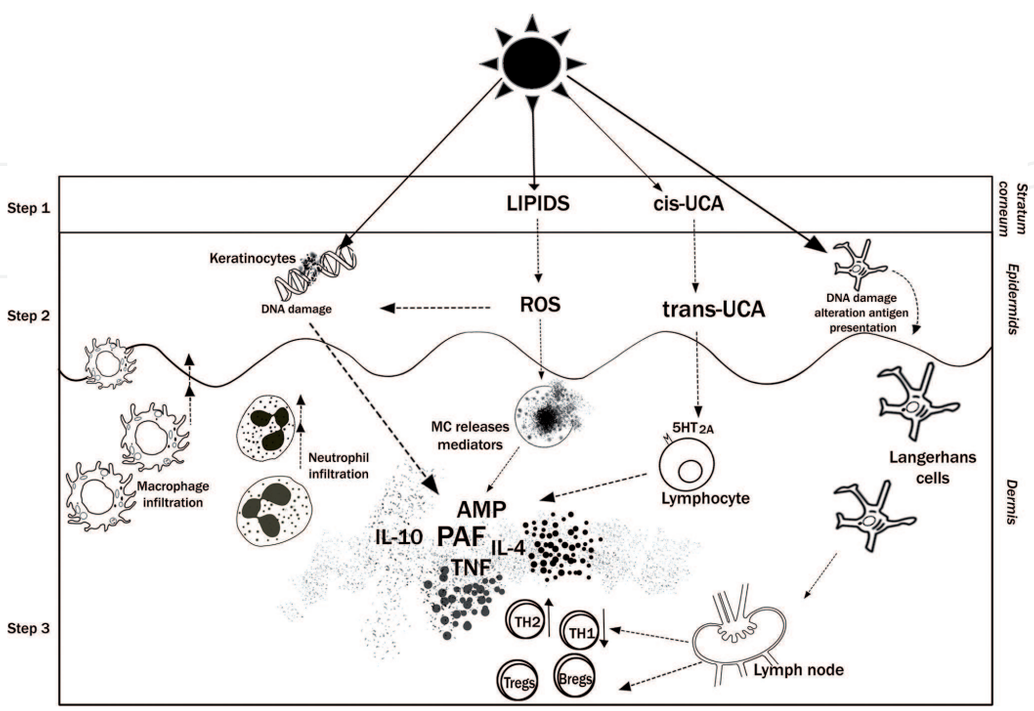


Figure 1.
The molecular mechanisms responsible for disruption of cellular immunity and some of the key events observed in the skin after the ultraviolet radiation exposure.

interleukin (IL)-10 by keratinocytes and other cells in the skin. The UVB waveband in particular also directly leads to isomerization of trans-UCA to cis-UCA. Cis-UCA induces immune suppression by binding to the 5-HT2A receptor, leading in turn to production of IL-10 by T-cells and B-cells. It may also indirectly lead to mast cell degranulation and stimulate the release of Platelet-Activating Factor (PAF). Formation of reactive oxygen species (ROS) by UVR not only induces and contributes to DNA damage but also directly stimulates PAF synthesis or the production of PAF-like molecules. UVR can also directly upregulate specific antimicrobial peptides (AMP) such as human beta-defensin-2, beta-defensin-3, S100A7, and RNase7 which are expressed by keratinocytes, lymphocytes, monocytes, and mast cells. These AMPs not only serve as initiators of innate immune response but they also communicate with the adaptive immune system and can activate it. The third step, as a result of the impact of UVR on the skin, is the appearance of an immunosuppressive microenvironment with abundance of TNF, IL-4 and IL-10 linked to Langerhans cell (LC) migration into lymph nodes and neutrophil and macrophage recruitment to the skin. As overall result, there is a modulation on T lymphocytes characterized by a global suppression of them and by a switch in the balance between two lymphocytes classes: the suppression of the Th1 population (implicated in immunity to intracellular organisms like viruses, through IL-2 and INF); an increase of Th2 (implicated in immunity against extracellular microbes such as bacteria, through IL-4/10) and an induction of Tregs and Bregs leading ultimately to functional immune suppression [67, 68].

4.3 Is UVR a cause of αHV recurrence?

A systematic epidemiological review was carried out in 2008 identifying 9 diseases that show sufficient evidence of a causal relationship with UVR exposure. These include the reactivation of the HSV. The other diseases are: melanoma, squamous cell carcinoma of the skin, basal cell carcinoma, solar keratoses, sunburns, cataracts, pterygium, squamous cell carcinoma of the cornea and conjunctiva [52]. In medical scientific literature several works have been published demonstrating the recurrence of αHV after exposition to solar UVR (sUVR) or experimental UVR (eUVR) both on human [69–74] and on animal models; [75, 76] due to these reasons most dermatology manuals recommend using sunscreen to avoid HSV recurrence [77]. Several papers have shown a correlation between UV exposure and occurrence of HSV-1 [74, 78]. Approximately the 25–50% of HL are attributed, at least in part, to sUVR exposure. In one scientific article it was shown that the use of sunscreen alone versus placebo showed 95–100% suppression of HL recurrences in 2 crossover trials after application of 4 Minimal Erythema Doses (MED) of eUVR [70, 79]. To evaluate the role of exposure to sUVR in primary and recurrent HSV-1 infections, the self-reported cause of infection among diagnosed patients in Hyogo Prefecture, Japan, was investigated. Among 4295 infected patients, 3678 had HSV-1, and 2656 of those patients (72.2%) had a recurrent flare-up. Sun-induced HSV-1 flare-up was reported by 10.4% of the total study population. However, this increased to 19.7% among patients diagnosed in July and August, to 28% among patients younger than 30 years diagnosed in July and August, and to 40% among patients younger than 30 years diagnosed in July and August with a recurrent infection [32]. Although these studies did not analyze HG, data from another study show that HG recurrences also occur more easily after exposure to UV rays. For example, one study found that patients with HG—in this case, on the buttocks—were likely to experience recurrences shortly after being exposed to eURV. Another study on HO compared the reactivation with sUVR, detecting an increase in reactivation in more exposed subjects, actually even if data are unclear due to confounding factors that can be superimposed, such as in particular the stress that might act both directly determining reactivation

and indirectly probably creating a greater need to expose to the sun [80]. As far as the VZV is concerned, one work reported a higher incidence of total HZ cases and cases of zoster in males during summer (from July to September) with a significant increase in May–June in patients studied in 1992–1998 in Ferrara in north-east Italy [81]. Another work shows the incidence of HZ peak for all subjects and for males it coincides with the maximum UVR months in summer. This association was not found for women, considered alone. It has not been explained why this difference should occur between men and women, but one possible explanation could be that older men tend to have more activities outside than women, such as gardening or walking, and therefore more exposure to sUVR. In addition to the increase in the incidence of zoster in summer, there was a significant increase over the same period in cases where lesions occurred on the face were compared to body sites normally covered [8]. In addition to considering the possible influence of the seasons on the incidence of αHV mucocutaneous lesions, some studies have succeeded in demonstrating a correlation with the UVR dose, geographical location, age and the body location. A dose of eUVR capable of triggering the recurrence of HL, is 4 MED, which corresponds to 80 min of sun exposure around 12 in July, at sea level taken by an individual with unprotected fair skin [70]. In some works, a slight latitudinal gradient of HL and a peak of prevalence in adulthood are demonstrated [82–84]. Another work highlighted the photolocalization of viral exanthema by observing a particular distribution of skin lesions, especially for VZV and HSV, between exposed areas and areas covered by clothes, preferring a location exposed to rays [85]. The recurrence time of HL after eVR exposure may be immediate (within 48 h) or delayed (after 2–7 days); [78] the time required for virus reactivation at the latency site [86], virus transport to the skin surface (it is estimated that the speed, demonstrated in vitro, is 3–5 mm/h)] and the virus replication in the epithelium with production of typical lesions (>24 h) [87, 88]. The eUVR had a beneficial effect on the virulence of HSV in an animal model. In fact, in a study it has been shown that 80% of mice irradiated before infection, and then re-irradiated several weeks later, developed recrudescent lesions. Only 20% of equivalent mice had not been irradiated before infection, but when irradiated after infection developed recrudescences [85].

4.4 How does solar radiation stimulate viral reactivation?

The exposure to sunlight has been associated with HSV reactivation [89–91]. It has been observed that 30% of causes of reactivation and axon migration to the skin are due to sudden exposure to sunlight and this seems also linked to the triggering of various mechanisms. There are many ways in which UV exposure is thought to impact αHV, and HSV recurrence in particular, directly through 3 pathways and probably also indirectly with unknown methods [85]. The first pathway is the depression of immune response due to UV exposure. The second pathway by which UVR may affect recurrence is directly through HSV reactivation [80, 85]. The third pathway study molecular events that trigger reactivation. The first pathway is based on the hypothesis that the virus continually tends to migrate from the ganglion to the skin. According to this theory, the normal immune response is activated through cell-mediated mechanisms of lymphocytes and macrophages and through the release of cytokines. In this way most of the migrations of ganglion-to-skin viruses is suppressed, as they are represented by few viral units and because the system is already sensitized, preventing a clinically evident reactivation because the infection remains sub-clinical. In the first pathway, the exposure to UVR determines the imbalance and suppression of the immune system, in a dose-dependent manner, which triggers a series of events so that local control of the reactivation is lost causing some virions to escape from immune control and the disease becomes

manifest. It does not seem that through this mechanism we can identify a "remote" influence that reactivates the virus, but only a local effect of more peripheral virions approaching the skin. In the second pathway, UVR directly determine an imbalance or radiation damage to epidermal and dermal cells, which are stimulated to repair producing transcription factors that in addition to activating cellular gene expression also activate the viral one and also inhibit the stimulus to apoptosis [80]. Especially the cell repair, through the c-Jun and c-Fos transcription factors, activates the HSV transcription promoter (infected cell polypeptide 0), leading to HSV transcription and reactivation [92]. Additionally, these repair pathways circumvent the activity of HSV latency-associated transcript preventing infected neurons from undergoing apoptosis and in turn, reactivating HSV [93]. Despite these models, significant gaps remain in our understanding of how these stimuli correlate with reactivation of the virus resulting in clinical disease. The third pathway is a molecular model that explains how UVR at the body surface results in multiple neuronal effects or hormonal alteration that could be relevant to reactivation. For example, a damage to innervated tissues that results in loss of the neurotrophin-producing cells and changes in the levels of regulatory neuropeptides, neurotrophins, neurotransmitters may occur following UV irradiation [94]. Nerve growth factor (NGF) deprivation was first found to trigger HSV reactivation in primary neuronal models of HSV latency using rat sympathetic neurons [95]. In vivo injection of anti-NGF serum into latently infected rabbits has also been shown to enhance reactivation of HSV [96]. Furthermore, interruption of signals downstream of the NGF receptor triggered reactivation in a variety of in vitro models of HSV latency [97–100], and has been shown to enhance explant mediated reactivation ex vivo [101, 102]. In addition, UV treatment in mice results in increased serum levels of cortisol and may act through a pathway that is similar to psychological stress-induced reactivation. It was also noted that the dexamethasone, a synthetic corticosteroid, stimulates reactivation of HSV-1 both ex vivo and in primary neuronal cultures, and the closely related bovine HSV-1 can also be reactivated in latently infected calves by intravenous injection of dexamethasone [98, 101, 103].

4.5 Do sun-screen reduce HSV recurrence?

To date four studies have been published on sunscreen used by volunteers who suffered from HL, two studies in which subjects were exposed to eUVR and two to sUVR. Two randomized controlled trials with a crossover design demonstrated, using a solar simulator, the effectiveness of lip sunscreen in reducing HL after UV exposure. The first study was conducted on 38 patients: it showed that after exposure to artificial ultraviolet, equal to 4 MED, HL developed in 27 patients (71%) treated with placebo. In contrast, when a sun protection factor (SPF) 15 sunscreen was applied during UV exposure, no lesion developed on 35 patients [70]. The second work carried out on 19 individuals, exposed to 4 MED for 10 min of ultraviolet light under artificial conditions, found that sunscreen significantly reduces relapses compared to placebo: one on 19 patients (5%) with sun protection against 11 out of 19 individuals (58%) with placebo [79].

Studies carried out in the natural environment have given different results.

The first work has been carried out in natural conditions in three ski resorts: Park City, Utah (January 21–28) SnowMass, Colorado (February 25 to March 3) and Keystone, Colorado (April 8–15) at a latitude between 40 and 39°. Fifty-one volunteer skiers were analyzed, showing that a SPF 15 sun screen compared to placebo was not effective to prevent reactivation of the virus. HL developed in 3 out of 24 subjects using protection and in 3 out of 27 with placebo [104]. This work was criticized by stating that the UV dose received by volunteer skiers during the trial was 1–3 MED

per day, which is lower than the 4 MED needed to trigger recurrence [70]. Probably due to this limitation, this study is not mentioned in the main guidelines for HL treatment [105]. Furthermore, it is not reported what amount of sunscreen was applied by skiers. However, in the latter two experiments carried out with artificial light the sunscreens were likely applied in a dose sufficient to respect the SPF value [106]. The second randomized, crossover study was carried out in northern Sardinia (Italy) on 20 volunteers who went to beach at a latitude of 40–41° using a sunblock stick with SPF 30. The study was conducted between May and July 2017 around the summer solstice (June 21st) when the sun reaches its highest point in the sky, to make the total amount of solar irradiance equal in the two sequential study periods. For each volunteer the study period lasted 60 days: 30 with protection and 30 without protection. The month with or without product application was randomly assigned to each patient so as 10 subjects started the trial without protection and 10 with protection and the opposite during the following month. During the month when volunteers had to use a protection, they were requested to apply the sunblock stick on the vermilion and lip skin two times consecutively creating a double protective layer before going out or going to the sea. The protection was repeated every 2 h, after eating or drinking, smoking and after a swim. 4 MED were reached and exceeded by volunteers several times during the 2 months of study. In fact, each volunteer remained at the beach at around 12 am with an average of 4.5 ± 0.95 h in the period with stick and 4.3 ± 0.94 h in the period without stick exceeding the aforementioned dose. Results demonstrated that sunscreen is effective in protecting the upper lip from reactivating the HL. In fact, only one volunteer out of 20 had a HL during the period of sunscreen use versus 10 out of 20 without sunscreen during the studied period. One volunteer from the second group reported two sequential HL. The single event during the period with labial photoprotection was unleashed in the last week, the 11 events of the period without photoprotection appeared from the second week of exposure. All lesions were clinically diagnosed with the help of Tzanck's cytodiagnostic examination [107]. In summary, these three studies, even though with a small number of subjects, showed that sunscreens can reduce the relapses caused by HSV following UVR exposure both in the laboratory and in the open air.

5. Treatment

If you suffer from relapsing HSV or you want to reduce the risk of the onset of HZ especially in summer, the most effective way is to avoid sunlight. Obviously, this is not always possible for most people. Even if someone deliberately avoids going to the beach, the face and other exposed parts of the body will still come in contact with direct sunlight throughout the day. What should be done to avoid solar radiation or minimize its effects?

5.1 Practical photoprotection strategy

To minimize the risk of a HS recurrence it is necessary: to perform a gradual and progressive sun exposure; to know what garments to wear; to know the environmental conditions of exposure; to know each skin phototype; to use a protective product against UVB and UVA with SPF suitable for each phototype and environmental conditions. Sun exposure must be gradual and progressive. The ideal would be a tanning obtained with irradiation times that do not induce erythema for long periods, in order to activate mechanisms of natural photoprotection. In fact, it has been shown that sub-erythematous doses of UVB produce a tan. It is advised wearing long trousers and long-sleeved shirts during summer to

avoid exposing more skin than necessary to direct sunlight and also a hat to protect the face from direct sunlight and to prevent lips and face from coming into direct contact with UVR. However, a garment does not offer a complete UV barrier. If it is wet, it has less dry effect in stopping UV. Dark colors absorb more UVR, while clear colors are more effective against IR. Cotton has a low protective factor compared to silk and blue jeans. We must therefore choose thick and darker fabrics to have an effective protection such as blue jeans. The effects of solar radiation also vary according to environmental conditions. For example, the amount of UVR in the environment varies during the day (maximum value between 12 and 16), in the different months of the year (period with more irradiation June–July–August in the northern hemisphere), in relation to the altitude (the quantity increases by 6% every km of height) and at the latitude (greater quantity in the tropics). When the sky is uniformly covered there is a reduction of about 50% of the UVR compared to the clear sky, but if it is partially cloudy the irradiation is not uniform and may decrease or increase depending on the shape and properties of the clouds. In the environment, in addition to direct rays, also the reflected ones might be taken: the reflection is 80% on the snow (almost 100% if the snow is fresh and compact), 20% in the water, 17% on the sand and 3% on the grass. In addition, the water works as a lens and we must remember that if you are immersed up to 40–50 cm 5% of the rays affects us by reflection even on those parts of the skin (area under the chin, inside the arms, under the buttocks) which usually are not exposed. In addition, artificial UV exposure such as tanning beds and other devices that produce UVR should be avoided. The phototype indicates the ability to defend against the UVR that varies from individual to individual. It can be easily obtained taking into account the color of the complexion, the eyes and the hair and also the reaction of the skin to the sun exposure. The lower skin types (blond, red hair with fair skin that hardly tans) are those who do not adapt to sun exposure and are subjected to skin damage. It is also important to protect daily the skin and the HV recurrence zones with a sunscreen.

5.2 Sunscreens

Sunscreen is a lotion, spray, gel or other topical product that absorbs or reflects some of the sun's UVR and thus helps protect against sunlight.

Depending on the mode of action, sunscreens can be classified into physical sunscreens (i.e. those that reflect the sunlight) or chemical sunscreens (i.e. those that absorb the UVR). Chemical, organic sunscreens absorb over relatively narrow wavebands, mainly in the UVB but nowadays also extending into the UVA. Physical sunscreens are inorganic substances that reflect and scatter both UV and visible radiations [107]. Use of sunscreen can reduce chronic damaging and the carcinogenic effects of UV radiation and recurrence of cutaneous HV.

Currently, it is recommended to spread the sunscreen on the skin in two layers in such a way that its thickness is as close as possible to 2 mg/cm^2, which is what enables to achieve the expected SPF. In practice, however, only between 0.5 and 1.5 mg/cm^2 are used mostly because of the high price of sunscreen. The effect of application thickness is shown diagrammatically in 34 for the ideal scenario of uniform application. This demonstrates how light absorption depends strongly on thickness. For example, a sunscreen labeled SPF 16 is reduced to an SPF of 2 if the consumer applies 0.5 mg/cm^2. Uniformity of application is another related crucial factor. The same amount of sunscreen non-uniformly applied implies that some areas receive little or no sunscreen. In general, sun lotions should always be applied in abundant quantities, in 2 layers and repeated during the day, immediately after swimming and every 2 h if sweating occurs. Only after a few days it will it be possible to reduce the SPF of the cream used, once the skin has had the time

to activate its defense systems. Use of sunscreen should never be interrupted, even once tanned, because the melanin filters 70% of the UVB but not the UVA and because over time its filtered capacity becomes less effective. The SPF is important in the choice of a solar product and the one suitable for each phototype should be increased if environmental conditions require it. The SPF is the ratio of the dose of UV radiation causing minimal erythema in unprotected skin to the dose which causes a minimal erythema in skin protected by the sunscreen. For example, if the normal MED is 30 mJ/cm^2 and the MED of the protected skin is 450 mJ/cm^2, the SPF is 15. In other words, application of sunscreen has caused an increase by a factor of 15 in the dose required to induce erythema. The SPF is principally a measure of the sunscreen UVB attenuation. Although conceptually very simple, it is often misunderstood by the general public, who think that using a high factor sunscreen will protect the skin against the harmful effects of UV radiation. Even if the sunscreen provides the protection indicated by the SPF, a day's exposure outdoors wearing a factor 15 sunscreen will still result in more than one MED for many individuals. This misconception often leads individuals to stay in the sun longer than they should. There is also a major difference between the highly controlled conditions in the sunscreen laboratory and outdoor real-life product use. [107]

6. Conclusion

Sunlight is the most common trigger in stimulating the HSV reactivation. It still not well known how the UVR determines the reactivation of the virus. Several hypotheses have been made but do not lead to a single common path with the other triggers. However, we know how to protect ourselves from solar radiation and what methods to use to avoid it or reduce its harmful effect on the skin.

Acknowledgements

The authors thank Angela Sabalic for her precious collaboration and the preparation of the figure and Giustina Casu for native language check and editing.

Conflict of interest

No conflict of interests is declared.

Author details

Vittorio Mazzarello*, Marco Ferrari, Stefano Decandia and Maria Alessandra Sotgiu
Skin Lab, Department of Biomedical Sciences, University of Sassari, Sassari, Italy

*Address all correspondence to: vmazza@uniss.it

IntechOpen

© 2018 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. CC BY

References

[1] Pellet P, Roizman B. The family Herpesviridae: A brief introduction. In: Fields BN, Knipe DM, Howley PM, editors. Fields Virology. 5th ed. Lippincott Williams & Wilkins: Philadelphia; 2007. pp. 2479-2499

[2] Davison AJ, Eberle R, Ehlers B, Hayward GS, McGeoch DJ, Minson AC, et al. The order Herpesvirales. Archives of Virology. 2009;**154**(1):171-177

[3] Xu F, Schillinger JA, Sternberg MR, et al. Seroprevalence and coinfection with herpes simplex virus type 1 and type 2 in the United States, 1988-1994. The Journal of Infectious Diseases. 2002;**185**(8):1019-1024

[4] Gross G et al. How to manage recurrent orofacial herpes simplex virus-1 lesions. The Pharmaceutical Journal. 2009;**283**(7565):187-190

[5] Fatahzadeh M et al. Human herpes simplex virus infections: Epidemiology, pathogenesis, symptomatology, diagnosis, and management November. JAAD. 2007;**57**(5):737-763

[6] Farooq AV, Shukla D. Herpes simplex epithelial and stromal keratitis: An epidemiologic update. Survey of Ophthalmology. 2012;**57**(5):448-462

[7] Schmader K. Herpes Zoster. Annals of Internal Medicine. 2018;**169**(3):ITC19-ITC31

[8] Zak-Prelich M, Borkowski JL, Alexander F, Norval M. The role of solar ultraviolet irradiation in zoster. Epidemiology and Infection. 2002;**129**(3):593-597

[9] Brisson M, Edmunds WJ, Law B, Gay NJ, Walld R, Brownell M, et al. Epidemiology of varicella zoster infection in Canada and the United Kingdom. Epidemiology and Infection. 2001;**127**:305-314

[10] Agelidis AM, Shuckla D. Cell entry mechanisms of HSV: What we have learned in recent years. Future Virology. 2015;**10**(10):1145-1154

[11] Steiner I, Kennedy PG, Pachner AR. The neurotropic herpes viruses: Herpes simplex and varicella-zoster. Lancet Neurology. 2007;**6**:1015-1028

[12] Lee GE, Murray JW, Wolkoff AW, Wilson DW. Reconstitution of herpes simplex virus microtubule-dependent trafficking in vitro. Journal of Virology. 2006;**80**:4264-4275

[13] Saksena MM, Wakisaka H, Tijono B, Boadle RA, Rixon F, Takahashi H, et al. Herpes simplex virus type 1 accumulation, envelopment, and exit in growth cones and varicosities in mid-distal regions of axons. Journal of Virology. 2006;**80**:3592-3606

[14] Smith GA, Gross SP, Enquist LW. Herpesviruses use bidirectional fast-axonal transport to spread in sensory neurons. Proceedings of the National Academy of Sciences of the United States of America. 2001;**98**:3466-3470

[15] Oh M, Akhtar J, Desai P, Shukla D. A role for heparan sulfate in viral surfing. Biochemical and Biophysical Research Communications. 2010;**391**(1):176-181

[16] Shukla D, Spear PG. Herpesviruses and heparan sulfate: An intimate relationship in aid of viral entry. The Journal of Clinical Investigation. 2001;**108**(4):503-510

[17] Spear PG, Manoj S, Yoon M, Jogger CR, Zago A, Myscofski D. Different receptors binding to distinct interfaces on herpes simplex virus gD can trigger events leading to cell fusion and viral entry. Virology. 2006;**344**:17-24

[18] Clement C, Tiwari V, Scanlan PM, Valyi-Nagy T, Yue BYJT, Shukla D.

A novel role for phagocytosis-like uptake in HSV entry. The Journal of Cell Biology. 2006;**174**(7):1009-1021

[19] Suzik JB, Cliffe AR. Strength in diversity: Understanding the pathways of herpes simplex virus reactivation. Virology. 2018;**522**:81-91

[20] Knipe DM, Cliffe A. Chromatin control of herpes simplex virus lytic and latent infection. Nature Reviews Microbiology. 2008;**6**:211-221

[21] Deshmane SL, Fraser NW. During latency, herpes simplex virus type 1 DNA is associated with nucleosomes in a chromatin structure. Journal of Virology. 1989;**63**:943-947

[22] Kubat NJ, Tran RK, McAnany P, Bloom DC. Specific histone tail modification and not DNA methylation is a determinant of herpes simplex virus type 1 latent gene expression. Journal of Virology. 2004;**78**:1139-1149

[23] Wang Q-Y, Zhou C, Johnson KE, Colgrove RC, Coen DM, Knipe DM. Herpesviral latency-associated transcript gene promotes assembly of heterochromatin on viral lytic-gene promoters in latent infection. Proceedings of the National Academy of Sciences of the United States of America. 2005;**102**:16055-16059

[24] Kwiatkowski DL, Thompson HW, Bloom DC. The Polycomb group protein Bmi1 binds to the herpes simplex virus 1 latent genome and maintains repressive histone Marks during latency. Journal of Virology. 2009;**83**:8173-8181

[25] Nicoll MP, Hann W, Shivkumar M, Harman LER, Connor V, Coleman HM, et al. The HSV-1 latency-associated transcript functions to repress latent phase lytic gene expression and suppress virus reactivation from latently infected neurons. PLoS Pathogens. 2016;**12**:e1005539

[26] Cliffe AR, Garber DA, Knipe DM. Transcription of the herpes simplex virus latency-associated transcript promotes the formation of facultative heterochromatin on lytic promoters. Journal of Virology. 2009;**83**:8182-8190

[27] Raja P, Lee JS, Pan D, Pesola JM, Coen DM, Knipe DM. A Herpesviral lytic protein regulates the structure of latent viral chromatin. MBio. 2016;**7**:e00633-16-10

[28] Leib DA, Bogard CL, Kosz-Vnenchak M, Hicks KA, Coen DM, Knipe DM, et al. A deletion mutant of the latency-associated transcript of herpes simplex virus type 1 reactivates from the latent state with reduced frequency. Journal of Virology. 1989;**63**:2893-2900

[29] Trousdale MD, Steiner I, Spivack JG, Deshmane SL, Brown SM, MacLean AR, et al. In vivo and in vitro reactivation impairment of a herpes simplex virus type 1 latency-associated transcript variant in a rabbit eye model. Journal of Virology. 1991;**65**:6989-6993

[30] Nadelman CM, Newcomer VD. Herpes simplex virus infections. Postgraduate Medicine. 2000;**107**:189-200

[31] Woo SB, Challacombe SJ. Management of recurrent oral herpes simplex infections. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics. 2007;**103** (S12 Suppl):e1-e18

[32] Ichihashi M, Nagai H, Matsunaga K. Sunlight is an important causative factor of recurrent herpes simplex. Cutis. 2004;**74**(5 Suppl):14-18

[33] Ship II, Morris AL, Durocher RT, Burkett LW. Recurrent aphthous ulcerations and recurrent herpes labialis in a professional school student population. Oral Surgery, Oral Medicine, and Oral Pathology. 1960;**13**:1191-1202

[34] Cohen SR, Goodacre A, Lim S, Johnston J, Henssler C, Jeffers B, et al. Clinical outcomes and complications associated with fractional lasers: A review of 730 patients. Aesthetic Plastic Surgery. 2017;**41**(1):171-178

[35] Miller CS, Cunningham LL, Lindroth JE, Avdiushko SA. The efficacy of valacyclovir in preventing recurrent herpes simplex virus infections associated with dental procedures. Journal of the American Dental Association (1939). 2004;**135**:1311-1318

[36] Begolli Gerqari A, Ferizi M, Kotori M, Daka A, Hapciu S, Begolli I, et al. Activation of herpes simplex infection after tattoo. Acta Dermatovenerologica Croatica. 2018;**26**(1):75-76

[37] Aldea S, Joly L-M, Roujeau T, Oswald A-M, Devaux B. Postoperative herpes simplex virus encephalitis after neurosurgery: Case report and review of literature. Clinical Infectious Diseases. 2003;**36**:96-99

[38] Cohen F, Kemeny ME, Kearney KA, Zegans LS, Neuhaus JM, Conant MA. Persistent stress as a predictor of genital herpes recurrence. Archives of Internal Medicine. 1999;**159**:2430-2436

[39] Glaser R, Kiecolt-Glaser JK. Stress-associated immune modulation and its implications for reactivation of latent herpesviruses. In: Glaser R, Jones J, editors. Human Herpesvirus Infections. New York: Dekker; 1994. pp. 245-270

[40] Stowe RP, Peek MK, Cutchin MP, Goodwin JS. Herpesvirus reactivation and socioeconomic position: A community-based study. Journal of Epidemiology and Community Health. 2010;**64**:666-671

[41] Glaser R, Kiecolt-Glaser JK. Chronic stress modulates the virus-specific immune response to latent herpes simplex virus type 1. Annals of Behavioral Medicine. 1997;**19**(2):78-82

[42] Pazin G, Ho M, Jannetta P. Reactivation of herpes simplex virus after decompression of the trigeminal nerve root. The Journal of Infectious Diseases. 1978;**138**:405-409

[43] Wung PK, Holbrook JT, Hoffman GS, Tibbs AK, Specks U, Min YI, et al. Herpes zoster in immunocompromised patients: Incidence, timing, and risk factors. The American Journal of Medicine. 2005;**118**(12):1416-1418

[44] Shirtcliff EA, Coe CL, Pollak SD. Early childhood stress is associated with elevated antibody levels to herpes simplex virus type 1. Proceedings of the National Academy of Sciences of the United States of America. 2009;**106**(8):2963-2967

[45] Steptoe A, Shamaci-Tousi A, Gylfe A, Henderson B, Bergstrom S, Marmot M. Socioeconomic status, pathogen burden and cardiovascular risk. Heart. 2007;**93**:1567-1570

[46] Glaser R, Kiecolt-Glaser JK. Stress-induced immune dysfunction: Implications for health. Nature Reviews Immunology. 2005;**5**(3):243-251

[47] Gray J, Wreghitt T, Pavel P, Smyth R, Parameshwar J, Stewart S, et al. Epstein-Barr virus infection in heart and heart–lung transplant recipients: Incidence and clinical impact. The Journal of Heart and Lung Transplantation. 1995;**14**(4):640-646

[48] Marks JG, Miller JJ. Lookingbill and Marks' Principles of Dermatology. Philadelphia: Saunders Elsevier; 2013

[49] Baron ED, Suggs AK. Introduction to photobiology. Dermatologic Clinics. 2014;**32**(3):255-266

[50] Schaefer H, Moyal D, et al. Recent advances in sun protection. Seminars in Cutaneous Medicine and Surgery. 1998;**17**(4):266-275

[51] Bolognia JL, Schaffer JV, Duncan KO, et al, editors. Dermatology Essentials. Oxford: Saunders/Elsevier; 2014

[52] Lucas RM et al. Estimating the global disease burden due to ultraviolet radiation exposure. International Journal of Epidemiology. 2008;**6**(37):654-667

[53] Runger MT. Ultraviolet light. In: Bolognia JL, Jorizzo JL, Schaffer JV, editors. Dermatology. Philadelphia: Elsevier Saunders; 2012. pp. 1455-1465

[54] Schwarz T, Halliday GM. Photoimmunology. In: Lim HW, Honigsmann H, Hawk JLM, editors. Photodermatology. New York: Informa Healthcare USA; 2007. pp. 55-74

[55] Mehling A, Loser K, Varga G, et al. Overexpression of CD40 ligand in murine epidermis results in chronic skin inflammation and systemic autoimmunity. The Journal of Experimental Medicine. 2001;**194**:615-628

[56] Casciola-Rosen LA, Anhalt G, Rosen A. Autoantigens targeted in systemic lupus erythematosus are clustered in two populations of surface structures on apoptotic keratinocytes. The Journal of Experimental Medicine. 1994;**179**:1317-1330

[57] Elmets CA, Bergstresser PR, Tigelaar RE, Wood PJ, Streilein JW. Analysis of the mechanism of unresponsiveness produced by haptens painted on skin exposed to low dose ultraviolet radiation. The Journal of Experimental Medicine. 1982;**158**:781-794

[58] Schwarz T. 25 years of UV-induced immunosuppression mediated by T cells-from disregarded T suppressor cells to highly respected regulatory T cells. Photochemistry and Photobiology. 2008;**84**:10-18

[59] Schweintzger N, Gruber-Wackernagel A, Reginato E, Bambach I, Quehenberger F, Byrne SN, et al. Levels and function of regulatory T cells in patients with polymorphic light eruption: Relation to photohardening. The British Journal of Dermatology. 2015;**173**:519-526

[60] Schweintzger NA, Gruber-Wackernagel A, Shirsath N, Quehenberger F, Obermayer-Pietsch B, Wolf P. Influence of the season on vitamin D levels and regulatory T cells in patients with polymorphic light eruption. Photochemical & Photobiological Sciences. 2016;**15**:440-446

[61] Byrne SN, Beaugie C, O'sullivan C, Leighton S, Halliday GM. The immune-modulating cytokine and endogenous Alarmin interleukin-33 is upregulated in skin exposed to inflammatory UVB radiation. The American Journal of Pathology. 2011;**179**:211-222

[62] Toews GB, Bergstresser PR, Streilein JW. Epidermal Langerhans cell density determines whether contact hyper sensitivity or unresponsiveness follows skin painting with DNFB. Journal of Immunology. 1980;**124**:445-453

[63] Noonan FP, Bucana C, Sauder DN, DeFabo EC. Mechanism of systemic immunesuppression by UV irradiation in vivo. II. The UV effects on number and morphology of epidermal Langerhans cells and the UV-induced suppression of contact hypersensitivity have different wavelength dependencies. Journal of Immunology. 1984;**132**:2408-2416

[64] Hart PH, Grimbaldeston MA, Finlay-Jones JJ. Sunlight, immunosuppression and skin cancer: Role of histamine and mast cells. Clinical and Experimental Pharmacology & Physiology. 2001;**28**:1-8

[65] van der Molen RG, Out-Luiting C, Claas FH, et al. Ultraviolet-B radiation induces modulation of antigen presentation of herpes simplex virus by human epidermal cells. Human Immunology. 2001;**62**(6):589-597

[66] Norval M. The effect of ultraviolet radiation on human viral infections. Photochemistry and Photobiology. 2006;**82**(6):1495-1504

[67] Patra V, Byrne SN, Wolf P. The skin microbiome: Is it affected by UV-induced immune suppression? Front Microbiol. 2016;**10**(7):1235

[68] Termorshuizen F, Garssen J, Norval M, Koulu L, Laihia J, Leino L, et al. A review of studies on the effects of ultraviolet irradiation on the resistance to infections: Evidence from rodent infection models and verification by experimental and observational human studies. International Immunopharmacology. 2002;**2**(2-3):263-275

[69] Spruance SL. Herpes simplex labialis. In: Sacks SL, Straus SE, Whitley RJ, Griffiths PD, editors. Clinical Management of Herpes Viruses. 4th ed. Amsterdam: IOS Press; 1995. pp. 11-20

[70] Rooney JF, Bryson Y, Mannix ML, et al. Prevention of ultraviolet-light-induced herpes labialis by sunscreen. Lancet. 1991;**338**(8780):1419-1422

[71] Duthie MS, Kimber I, Norval M. The effects of ultraviolet radiation on the human immune system. The British Journal of Dermatology. 1999;**140**:995-1009

[72] Laihia JK, Jansen CT. Solar-simulating ultraviolet irradiation of the skin of human subjects in vivo produces Langerhans cell responses distinct from irradiation ex vivo and in vitro. Experimental Dermatology. 2000;**9**:240-247

[73] Termorshuizen F, Garssen J, Norval M, et al. A review of studies on the effects of ultraviolet irradiation on the resistance to infections: Evidence from rodent infection models and verification by experimental and observational humane studies. International Immunopharmacology. 2002;**2**:263-275

[74] Perna JJ, Mannix ML, Rooney JF, Notkins AL, Straus SE. Reactivation of latent herpes simplex virus infection by ultraviolet light: A human model. Journal of the American Academy of Dermatology. 1987;**17**:473-478

[75] Norval M, El-Ghorr AA. UV radiation and mouse models of herpes simplex virus infection. Photochemistry and Photobiology. 1996;**64**(2):242-245

[76] Laycock KA, Lee SF, Brady RH, et al. Characterization of a murine model of recurrent herpes simplex viral keratitis induced by ultraviolet B radiation. Investigative Ophthalmology & Visual Science. 1991;**32**(10):2741-2746

[77] James W et al. Andrews' Diseases of the Skin Clinical Dermatology. 11th ed. Philadelphia: Saunders-Elsevier; 2011

[78] Spruance SL, Freeman DJ, Stewart JC, McKeough MB, Wenerstrom LG, Krueger GG, et al. The natural history of ultraviolet radiation-induced herpes simplex labialis and response to therapy with peroral and topical formulations of acyclovir. The Journal of Infectious Diseases. 1991;**163**:728-734

[79] Duteil L, Queille-Roussel C, Loesche C, Verschoore M. Assessment of the effect of a sunblock stick in the prevention of solar-simulating ultraviolet light-induced herpes labialis. Journal of Dermatological Treatment. 1998;**9**(1):11-14

[80] Ludema C, Cole SR, Poole C, Smith JS, Schoenbach VJ, Wilhelmus KR. Association between unprotected

ultraviolet radiation exposure and recurrence of ocular herpes simplex virus. American Journal of Epidemiology. 2014;**179**(2):208-215

[81] Gallerani M, Manfredini R. Seasonal variation in herpes zoster infection. The British Journal of Dermatology. 2000;**142**:588-589

[82] Young TB et al. Cross-sectional study of recurrent herpes labialis. Prevalence and risk factors. American Journal of Epidemiology. 1988;**127**:612-625

[83] Axell T et al. Occurrence of recurrent herpes labialis in an adult Swedish population. Acta Odontologica Scandinavica. 1990;**48**:119-123

[84] Reichart PA. Oral mucosal lesions in a representative cross-sectional study of aging Germans. Community Dentistry and Oral Epidemiology. 2000;**28**:390-398

[85] Norval M, el-Ghorr A, Garssen J, Van Loveren H. The effects of ultraviolet light irradiation on viral infections. The British Journal of Dermatology. 1994;**130**(6):693-700

[86] Openshaw H, Asher LVS, Wohlenberg C, Sekizawa T, Notkins AL. Acute and latent infection of sensory ganglia with herpes simplex virus. Immune control and virus reactivation. The Journal of General Virology. 1979;**44**:205-215

[87] Lycke E, Kristensson K, Svennerholm B, Vahine A, Ziegler R. Uptake and transport of herpes simplex virus in neurites of rat dorsal root ganglia cells in culture. The Journal of General Virology. 1984;**65**:55-64

[88] Blank H, Haines H. Experimental human reinfection with herpes simplex virus. The Journal of Investigative Dermatology. 1973;**61**:223-225

[89] Chida Y, Mao X. Does psychosocial stress predict symptomatic herpes simplex virus recurrence? A meta-analytic investigation on prospective studies. Brain, Behavior, and Immunity. 2009;**23**:917-925

[90] El Hayderi L, Delvenne P, Rompen E, Senterre JM, Nikkels AF. Herpes simplex virus reactivation and dental procedures. Clinical Oral Investigations. 2013;**17**:1961-1964

[91] Padgett DA, Sheridan JF, Dorne J, Berntson GG, Candelora J, Glaser R. Social stress and the reactivation of latent herpes simplex virus type 1. Proceedings of the National Academy of Sciences of the United States of America. 1998;**95**:7231-7235

[92] Loiacono CM, Taus NS, Mitchell WJ. The herpes simplex virus type 1 ICP0 promoter is activated by viral reactivation stimuli in trigeminal ganglia neurons of transgenic mice. Journal of Neurovirology. 2003;**9**:336-345

[93] Henderson G, Peng W, Jin L, et al. Regulation of caspase 8- and caspase 9-induced apoptosis by the herpes simplex virus type 1 latency-associated transcript. Journal of Neurovirology. 2002;**8**(suppl 2):103-111

[94] Stefanato CM, Yaar M, Bhawan J, Phillips TJ, Kosmadaki MG, Botchkarev V, et al. Modulations of nerve growth factor and Bcl-2 in ultraviolet-irradiated human epidermis. Journal of Cutaneous Pathology. 2003;**30**:351-357

[95] Wilcox CL, Johnson EM. Nerve growth factor deprivation results in the reactivation of latent herpes simplex virus in vitro. Journal of Virology. 1987;**61**:2311-2315

[96] Hill JM, Garza HH, Helmy MF, Cook SD, Osborne PA, Johnson EM, et al. Nerve growth factor antibody

stimulates reactivation of ocular herpes simplex virus type 1 in latently infected rabbits. Journal of Neurovirology. 1997;**3**:206-211

[97] Camarena V, Kobayashi M, Kim JY, Roehm P, Perez R, Gardner J, et al. Nature and duration of growth factor signaling through receptor tyrosine kinases regulates HSV-1 latency in neurons. Cell Host & Microbe. 2010;**8**:320-330

[98] Cliffe AR, Arbuckle JH, Vogel JL, Geden MJ, Rothbart SB, Cusack CL, et al. Neuronal stress pathway mediating a histone methyl/phospho switch is required for herpes simplex virus reactivation. Cell Host & Microbe. 2015;**18**:649-658

[99] Kobayashi M, Wilson AC, Chao MV, Mohr I. Control of viral latency in neurons by axonal mTOR signaling and the 4E-BP translation repressor. Genes & Development. 2012;**26**:1527-1532

[100] Linderman JA, Kobayashi M, Rayannavar V, Fak JJ, Darnell RB, Chao MV, et al. Immune escape via a transient gene expression program enables productive replication of a latent pathogen. Cell Reports. 2017;**18**:1312-1323

[101] Du T, Zhou G, Roizman B. Induction of apoptosis accelerates reactivation of latent HSV-1 in ganglionic organ cultures and replication in cell cultures. Proceedings of the National Academy of Sciences of the United States of America. 2012;**109**:14616-14621

[102] Messer HGP, Jacobs D, Dhummakupt A, Bloom DC. Inhibition of H3K27me3-specific histone demethylases JMJD3 and UTX blocks reactivation of herpes simplex virus 1 in trigeminal ganglion neurons. Journal of Virology. 2015;**89**:3417-3420

[103] Workman A, Eudy J, Smith L, da Silva LF, Sinani D, Bricker H, et al. Cellular transcription factors induced in trigeminal ganglia during dexamethasone-induced reactivation from latency stimulate bovine herpesvirus 1 productive infection and certain viral promoters. Journal of Virology. 2012;**86**:2459-2473

[104] Mills J, Hauer L, Gottlieb A, Dromgoole S, Spruance S. Recurrent herpes labialis in skiers: Clinical observations and effect of sunscreen. The American Journal of Sports Medicine. 1987;**15**:76-78

[105] Worrall G. Herpes labialis. BMJ Clinical Evidence. 2009;**2009**:1704

[106] Mazzarello V, Ferrari M, Piu G, Pomponi V, Solinas G. Do sunscreen prevent recurrent herpes labialis in summer? Journal of Dermatological Treatment. 2018;**23**:1-4

[107] Moseley H. Photoprotection. In: Ferguson J, Dover JS, editors. Photodermatology. 1st ed. London: Manson publishing; 2006. pp. 21-28