Dermatology Clinics & Research
DCR, 5(1): 206-211
www.scitcentral.com

ISSN: 2380-5609

Review Article: Open Access

Review of Methods and Mechanisms Involved with Local Hyperthermia in the Treatment of Condyloma Acuminatum

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Received May 27, 2019; Accepted May 29, 2019; Published June 05, 2019

ABSTRACT

Condyloma acuminatum (CA) is a sexually transmitted infection resulting from certain types of human papillomavirus (HPV). The manifestation of this infection may be found anywhere within the anal or genital area, frequently on external surfaces of the body, including the penile shaft, scrotum or labia majora as well as on internal surfaces like the urethra orifice, vagina, cervix or anus. Humans are the only natural host of HPV, which shows high tissue specificity and usually results from micro-trauma of the skin or mucosa through which the virus can infect the germinal keratinocytes. There exist many therapeutic options for the treatment of warts, such as topical imiquimod, cryotherapy, surgical excision and electrocautery. While all of these treatments show varying degrees of effectiveness, each possesses their own limitations. Recent evidence has indicated that thermotherapy, a method of heating local tissue to achieve a therapeutic effect, has been successful in the treatment of HPV-infected skin lesions. Here, we summarizes the possible mechanisms of local hyperthermia in the treatment of CA and briefly introduce the tools and methods involved in the application of this procedure.

Keywords: Hyperthermia, Immune response, Condyloma acuminatum, Human papilloma virus

INTRODUCTION

Human papillomavirus (HPV) comprises a group of common circular DNA viruses that exclusively infect human epithelial cells and produce a variety of clinical syndromes. Frequent manifestations of HPV include cutaneous lesions such as anogenital warts, benign papillomas and occasionally, cancers. Condyloma acuminatum (CA), which is the most common sexually transmitted infection, results from certain types of HPV. Current treatments for CA are generally associated with suboptimal recurrence rates, necessitating repeated treatments which add to the already negative impact on the patient's quality of life. Hyperthermia, a condition characterized by increased body temperature due to failed thermoregulation, elicits various effects on the physiology of living cells. For example, fever-range temperatures of 39-40°C can modulate activities of immune cells, including antigen-presenting cells, T-cells and natural killer cells. Heat shock temperatures of 41-43°C can increase tumor cell immunogenicity and cytotoxic temperatures of >43°C can create antigen sources to induce anti-tumor immune responses [1]. Use of hyperthermia in the treatment of various diseases generally involves an application of 40-44°C for 30-60 min. Hyperthermia with use of temperatures ranging from 39-45°C was found to be effective in treating some tumors and HPV infections [2], including common warts, palmoplantar warts and CA. Clinically, application of hyperthermia is directed at only one lesion site, selected as the target lesion for hyperthermia, with remaining untreated lesions obliterating following clearance of the target lesion. Such responses suggest that

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Citation: Wang Y, Niu X, Wu L, Li M, Du Y, et al. (2019) Review of Methods and Mechanisms Involved with Local Hyperthermia in the Treatment of Condyloma Acuminatum. Dermatol Clin Res, 5(1): 206-211.

hyperthermia may promote specific immune responses directed against HPV. The biological mechanisms involved with local hyperthermia in the treatment of HPV associated directed at understanding these mechanisms have focused on diseases have yet to be fully understood. As most studies directed at understanding these mechanisms have focused on inflammation and immunity, in this report, we discuss the effects of hyperthermia-related inflammatory and immunity responses from four perspectives: cytokines, cell apoptosis/signaling pathways, skin immune cells and proteins.

CYTOKINES

Hyperthermia induces a significant increase in the transcriptional expression of interferon in CA

Hyperthermia induces a significant increase in transcriptional expressions of interferon (IFN)-α, IFN-β and IFN-γ, in a temperature-dependent manner in CA [3]. IFNs, which can exert anti-viral, immunomodulatory and anti-cancer effects [4], comprise a small group of highly bioactive glycoproteins produced by human and animal cells when stimulated by pathogens or microorganisms. They consist of three different sub-types: type I IFNs (i.e., IFN-α/β) that are produced in virally infected cells and type II IFN (i.e., IFN-γ) that is not virus inducible and restricted to mitogen- or cytokine-activated lymphoid cells such as T-lymphocytes and natural killer (NK) cells. Type III interferon (IFN-λ) plays an important role in antifungal responses of neutrophils [5]. IFN-α and β transduce their signals through the sequential activation of IFN-α/β receptor (IFNAR) (with two subunits, IFNAR1 and IFNAR2)-associated Janus tyrosine kinases Jak1 and Tyk2, leading to tyrosine phosphorylation and activation of Stat1 and Stat2. Activated Stat1/Stat2 heterodimers then translocate to the nucleus, where they associate with the IFN regulatory factor IRF-9 to form an active complex (known as ISGF-3) on the IFN-stimulatory response element (ISRE). ISG blocks viral replication by presenting antigens and inhibiting viral RNA transcription or translation to establish antiviral responses in target cells [6]. OAS1 and PKR (one of the ISGs) are two main enzymes involved in antiviral activity in interferon-related pathways. It has been reported that hyperthermia up-regulates the expression of PKR and OASI and inhibits the proliferation of HPV virus [7]. The IFN-α/β receptor-related kinases, STAT1 and STAT2 are significantly increased after hyperthermia in CA.

Local hyperthermia decreases the expression of CCL-20 in CA

The mRNA expressions of CCL-20 in CA specimens were found to be significantly increased as compared with that in normal skin. Local hyperthermia at 42°C and 45°C significantly decreased these mRNA levels of CCL-20 [8]. CCL-20, a member of the chemokine family, participates in the migration of dendritic and T cells, plays a role in tumor immunity and autoimmune diseases and exerts robust broad-spectrum antimicrobial activity. CCL20 also plays an important role in regulating Langerhans cells (LCs) and their precursors to enter the epidermis [9]. CCL-20 expression was reported to be increased by TNF-a and IL-1a in oral squamous cell carcinomas, intestinal epithelial cells and keratinocytes [10]. Local hyperthermia reduces the expression of IL-α in CA tissue, followed by a decrease in the expression of CCL-20, thereby decreasing the number of epidermal LCs and promoting the migration of LCs to dermal lymph nodes. The chemokines CCL21 and CCL19, secreted by lymph node cells guide LCs to enter the T-cell region through CCL7 on the surface of LCs. LCs present antigens to antigen-specific T cells and stimulate immune effects of anti-viruses, which is conducive to the treatment of CA [8].

HYPERTHERMIA-RELATED APOPTOTIC SIGNALING PATHWAYS

The apoptosis-related factors - DR4, DR5, Fas, Bax and Bcl-2

Keratinocytes are located in the outermost region of the skin and remain stable after programmed death, as resulting from pathological conditions and external stimuli. Apoptosis is mainly regulated by mitochondria and death receptor pathways, with the Bcl-2 gene family acting as an important regulator of programmed cell death. The differential expression of anti-versus pro-apoptotic Bcl-family proteins determines the inherent susceptibility of a given cell to respond to apoptotic signals. The most important proteins of the Bcl-2 family are the pro-apoptotic Bax and anti-apoptotic Bcl-2 proteins and this ratio of Bcl-2/Bax represents a critical factor in the regulation of apoptosis [11]. The two putative apoptosis-inducing receptor-ligand systems, tumor necrosis factor (TNF) and CD95, have been shown to play a major role in many physiological and pathophysiological situations, as they induce apoptosis by activation of their corresponding receptors, Fas and TNFR-1. TRAIL, a member of the TNF family of cytokines, has been shown to induce apoptosis in a variety of transformed cell lines by binding to TRAIL receptors [12] and five distinct receptors for the TRAIL ligand have been identified: death receptor 4 (DR4), DR5, decoy receptor 1 (DcR1), DcR2 and osteoprotegerin (OPG). DR4 and DR5 contain death domains (DD) in their cytoplasmic region that can mediate cell apoptosis upon binding with the membrane form of TRAIL or with the soluble TRAIL [12]. In CA tissue, expression of the anti-apoptotic effects of Bcl-2 are decreased while that of the pro-apoptotic effects of Bax are increased after local hyperthermia at 42-45°C. In addition, expressions of Fas, DR4 and DR5 are increased after these same local hyperthermia conditions, indicating that the death receptor promotes apoptosis through activation of death receptor pathways [13]. Accordingly, hyperthermia

promotes apoptosis within HPV infected cells by affecting the expression of DR4, DR5, Fas, Bax and Bcl-2 and, in this way, plays an antiviral immune role.

EFFECT OF LOCAL HYPERTHERMIA ON CELLULAR FUNCTIONS

Local hyperthermia induces migrational maturation of Langerhans cells (LCs) in CA

It has been reported that local hyperthermia induces migrational maturation of Langerhans cells in CA [14]. LCs is dendritic cells (DCs) within the epidermis. These cells possess a robust ability to absorb and present antigens, but a weak ability to stimulate T-cell activation. When the antigen enters the epidermis, it induces epidermal cells to secrete a number of cytokines, among which interleukin (IL)-1β and tumor necrosis factor alpha (TNF-α) stimulate LCs migration to the dermis. Within the dermis, lymphatic endothelial cells secrete the chemokine, CCL21, which attracts LCs into lymphatic vessels and then enables these cells to flow into lymph nodes through the chemokine receptor CCR7 located on the surface of LCs. The LCs surface molecule, CCR7, interacts with the chemokine, CCL21 and CCL19, secreted by lymph node cells to induce LCs to enter the T-cell region. LCs present antigens to antigen-specific T-cells, and, in this way, play an immune role. Local hyperthermia, as administered at fever ranges, promotes the migration and activation of LCs in mice [15]. We have found similar effects of hyperthermia when administered in temperatures above that of fever ranges [14]. Further, local hyperthermia at 42 and 45°C concomitantly produces an increase in the expression of CCR7 and a decrease in the expression of CCR6, both of which are prerequisites for transport of LCs to regional lymph nodes [16].

HYPERTHERMIA INCREASES EDITING EFFICIENCY OF THE HPV GENE

Hyperthermia changes the nucleic acid composition of the HPV E2 gene

Although the E2 gene constitutes only a small portion of the total viral genome, E2 plays an important role in replication and transcription of HPV by binding to specific cognate sequences in the viral genome [17]. APOBEC, a family member which can induce cytosine deaminase activity within humans, consists of 11 members and is a natural defender of the human body. The antiviral agents of APOBEC, A3A and A3G, were initially identified as factors involved with limiting HIV-1 infection [18]. Recently, results from several high-profile studies have suggested that APOBEC3-mediated mutagenesis is highly enriched in HPV-positive cervical and head-and-neck cancers [19]. In addition, two antiviral agents of the human APOBEC3A (A3A) and A3G genes have been shown to be expressed in epithelial cells and both are reported to be involved in editing HPV by inducing a cytidine (C) to uracil (U) hyper mutation [20]. APOBEC can deaminate cytosine on the substrate by binding to DNA and RNA, thus mutating DNA or RNA. Overall, APOBEC3 exerts a wide range of antiviral functions and it has been reported that hyperthermia induces a significant increase of IFN in CA [21]. Such an effect can subsequently positively regulate APOBEC3 expression [22], to increases the expression of APOBEC A3 A and A3G in HPV infected cells. APOBEC both mutates the E2 gene of HPV (G→A, C→T) and destroys the function of the E2 gene which may, in part, serve as the basis for its thermotherapy effect in CA [23].

Hyperthermia changes HPV-6/11 E6 and E7 genes

In response to treatment with varying temperatures, we found that the expressions of HPV-6 E6/E7 and HPV-11 E6/E7 decreased as a function of increasing temperature [24]. Accordingly, this hyperthermia-induced reduction of E6 and E7 expression and inhibition of HPV proliferation may result from enhancing the effects of interferons and/or inhibiting viral gene replication [24].

RELATED PROTEINS

DNAJA4

The expression of heat shock protein is closely related to the pathophysiology of stress as can occur with elevated body temperature [25]. As one of the members of the DNAJ protein family, DNAJA4, with a molecular weight around 40 kDa, has been shown to function as a co-chaperone for HSP70 through its J domain and, in this way, can stimulate ATP-hydrolysis activity [26]. DNAJA4 can be induced in HaCaT cells, foreskin and CA tissues subjected to hyperthermia, as demonstrated at both transcriptional and translational levels [27]. Interestingly, the HPV E7 oncoprotein was reported to bind DnaJA3 to facilitate viral carcinogenesis [28]. Although no direct evidence exists showing associations between DNAJA4 and HPV oncoproteins, given the highly conserved structure among DnaJ protein family members, DNAJA4 may likely function as DNAJA3 in response to HPV infection. As a heat shock protein, DNAJA4 may provide a protective role in cells undergoing active proliferation and may also be utilized by HPV-infected keratinocytes to survive under conditions of hyperthermia. Nuclear Factor-kappa B (NF-kB) is an important transcription factor which initiates the transcription of multiple genes related to inflammation, immunity and cell survival and serves as a hyperthermia-responsive protein whose activity is altered during heat shock [29]. As increased HSP70 alters NF-kB activity [30], hyperthermia-induced heat shock proteins may be one of the regulators of cellular proliferation, immune responses and inflammation via the NF-kB pathway. Hyperthermia can induce the activity of NF-kB in keratinocytes, especially in keratinocytes lacking DNAJA4 [27]. The findings that

DNAJA4 was up regulated by 44°C hyperthermia treatment, a deficiency of which reduced HaCaT cell proliferation and altered cytokine expression, indicate effects which favor anti-viral activity, mainly through a NF-kB dependent pathway. In this way, DNAJA4 may serve as a very promising therapeutic target whose inhibition could contribute to the therapeutic efficacy of local hyperthermia treatment against HPV-infectious diseases.

Surviving

Calcium influx is required for the activation of cellular function. Store-operated calcium entry (SOCE) mediates calcium influx through a calcium release-activated calcium (CRAC) channel, which represents a principal calcium entry mechanism in non-excitable cells. Composed of Orai molecules in the plasma membrane, CRAC channels are activated by stromal interaction molecules (STIM) located in the membrane of the endoplasmic reticulum (ER). STIM proteins monitor changes in calcium concentrations within the ER and activate Orai molecules. There are two subtypes of STIM proteins, STIM1 and STIM2 [31]. STIM1 is an ER calcium sensor that responds to depleted levels of ER calcium. Decreases in ER calcium concentrations induce STIM1 multimerization and translocation into puncta close to the plasma membrane where STIM1 multimers bind to and activate the Orai channel, leading to a massive influx of calcium. During events related to immunity, calcium regulates cytoskeleton remodeling, release of vesicle contents and transcriptional changes. In addition, increased sustained cytosolic calcium results in cellular activation or apoptosis [32]. STIM1, which typically induces a robust calcium influx, is often over expressed in human cancers such as melanoma tissues, multiple melanoma cell lines, and cervical cancer [33]. Physiological processes such as the regulation of reactive oxygen species (ROS), mitochondrial damage and calcium overload can all influence apoptosis [34]. Calcium overload may damage mitochondria and result in the activation of the apoptotic signaling cascade [34]. It has been demonstrated that hyperthermia can activate CRAC channels and increase calcium influx. While such an effect can promote cell apoptosis in non-HPV infected cells, this process is not as obvious in HPV infected cells [35]. Caspase-3 is the essential death protease and final executor of calcium signaling, involved in the apoptotic pathway. Surviving, a member of the inhibitor of apoptosis protein (IAP) family, is abundantly expressed in some malignancies, but undetectable in normal adult tissues. Survive in binds to caspase-3 and inhibits caspase activity in cells exposed to a diverse array of apoptotic stimuli [36]. Survive in expression is likely to be regulated by HPV, as survive in expression levels are strongly dependent on continuous HPV E6/E7 expression and HPV E6/E7 is reported to trans activate the survivin promoter [37]. Based on these findings, we hypothesize that inhibition of this over expression of survive in may further improve the therapeutic effects of hyperthermia treatment in HPV-infected lesions.

SUMMARY

Here we present a review on the methods and mechanisms of local hyperthermia for the treatment of CA. We report that local hyperthermia has been shown to be successfully in the treatment of HPV infected skin lesions. The procedure is easy to apply and is associated with high cure and low recurrence rates. However, details regarding the molecular mechanisms of hyperthermia within the immune system remain a challenge for future investigation. This review summarizes several important aspects on the effects of hyperthermia in HPV infected cells and tissues. Such information will help in identifying the mechanisms of hyperthermia and serve as a foundation for procedures that can be used to optimize the conditions of local hyperthermia for the treatment of viral warts, tumors and other diseases.

FUNDING

This work was supported by the National Natural Science Foundation of China (81673070, 81872538) and 111 Project (D18011).

CONFLICT OF INTERESTS

The authors declare that they have no conflict of interest.

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