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Hypochlorous Acid: From Innate Immune Factor and Environmental Toxicant to Chemopreventive Agent Targeting Solar UV-Induced Skin Cancer

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A multitude of extrinsic environmental factors (referred to in their entirety as the 'skin exposome') impact structure and function of skin and its corresponding cellular components. The complex (i.e. additive, antagonistic, or synergistic) interactions between multiple extrinsic (exposome) and intrinsic (biological) factors are important determinants of skin health outcomes. Here, we review the role of hypochlorous acid (HOCl) as an emerging component of the skin exposome serving molecular functions as an innate immune factor, environmental toxicant, and topical chemopreventive agent targeting solar UV-induced skin cancer. HOCl [and its corresponding anion (OCl^-; hypochlorite)], a weak halogen-based acid and powerful oxidant, serves two seemingly unrelated molecular roles: (*i*) as an innate immune factor [acting as a myeloperoxidase (MPO)-derived microbicidal factor] and (*ii*) as a chemical disinfectant used in freshwater processing on a global scale, both in the context of drinking water safety and recreational freshwater use. Physicochemical properties (including redox potential and photon absorptivity) determine chemical reactivity of HOCl towards select biochemical targets [i.e. proteins (e.g. IKK, GRP78, HSA, Keap1/NRF2), lipids, and nucleic acids], essential to its role in innate immunity, antimicrobial disinfection, and therapeutic anti-inflammatory use. Recent studies have explored the interaction between solar UV and HOCl-related environmental co-exposures identifying a heretofore unrecognized photo-chemopreventive activity of topical HOCl and chlorination stress that blocks tumorigenic inflammatory progression in UV-induced high-risk SKH-1 mouse skin, a finding with potential implications for the prevention of human nonmelanoma skin photocarcinogenesis.

Keywords: hypochlorous acid, chlorination stress, environmental exposure, skin exposome, solar ultraviolet radiation, inflammation, skin cancer

INTRODUCTION: ENVIRONMENTAL EXPOSURE AND SKIN HEALTH: FOCUS ON SOLAR ULTRAVIOLET RADIATION AND CO-EXPOSURE TO ENVIRONMENTAL TOXICANTS

Skin, the largest part of the human integumentary system constituting about 15% of the total adult body mass, is positioned at the interface between environment and the body's internal organs (1). The skin is a crucial and dynamic barrier against the constantly changing environment, autonomously maintaining organ-level and systemic homeostasis. As one of the key barriers of defense against physical, chemical, and microbial stressors, the skin is a complex organ functioning in tissue regeneration and wound healing, hydro-, osmo-, and thermoregulation, endocrine and sensory functions, biosynthesis, metabolism, innate and adaptive immunity, circadian rhythmicity, and neuro-psychosocial communication (1–8). Among various environmental factors relevant to human health, solar exposure is known to impact tissue homeostasis modulating many of these cutaneous functions. Indeed, skin barrier dysfunction is a hallmark of numerous cutaneous pathologies including allergic reactions, microbial infection, photoaging, and photocarcinogenesis.

As an outer surface organ, human skin is ubiquitously exposed to solar ultraviolet (UV) radiation. UV exposure has both positive and negative effects on human health (9). It is responsible for the biosynthesis of vitamin D_3, can stimulate the production of photoprotective melanin, and is used therapeutically to treat inflammatory skin diseases (such as psoriasis, vitiligo, localized scleroderma, and atopic dermatitis). At the same time, solar UV is a potent environmental human carcinogen (10–12). The mechanisms by which solar UV-radiation causes skin photodamage are wavelength-dependent (11). UVB (290-320 nm) is thought to cause direct structural damage to DNA in the form of epidermal cyclobutane pyrimidine dimers (CPDs) and other photoproducts. Most of the solar UV energy incident on human skin derives from the deeply penetrating UVA region (≥ 95%, 320-400 nm) not directly absorbed by DNA, and UVA-induced photodamage occurs by oxidative mechanisms mediated by reactive oxygen species (ROS). Contributing to the adverse effects of solar UV exposure is its known action as a systemic immunosuppressant, compromising an individual's immune response with mechanistic implications for photocarcinogenesis (13).

UV and other environmental toxicants can be conceptualized as components of the overall skin exposome (**Figure 1**), a term integrating all environmental cutaneous exposures and consequent biological effects including antagonism and potentiation that may result from co-exposures (14): (*i*) physical (such as thermal and mechanical trauma), (*ii*) chemical/xenobiotic [such as industrial pollutants, topical and systemic drugs, disinfectants, pharmaceuticals and personal care products (PPCPs)], (*iii*) microbiomic (originating from commensal and pathogenic microbes), (*iv*) allergenic (either of chemical or biological nature), and (*v*) life style-associated (such as tobacco product use, dietary choices, circadian rhythmicity, sleep pattern etc.) factors. Importantly, the complete skin exposome is subject to cross-talk with intrinsic factors (i.e. an individual's primary biological determinants of skin structure and function) including: (*i*) genetics (as associated with ethnicity, sex as a biological variable (SABV), disease vulnerabilities etc.), (*ii*) pathobiological occurrences [such as infections, metabolic dysregulation (including diabetes), and autoimmune disturbances], and (*iii*) chronological aging (7, 15–20). Certain aspects and subcategories of the skin exposome have been expertly reviewed including the skin microbiome and the skin redoxome (7, 8).

Molecular crosstalk and mechanistic overlap between various components of the extrinsic skin exposome is well substantiated at the molecular level. For example, potentiation of solar UV-induced cutaneous and systemic injury by co-exposure to other environmental toxicants/pollutants has attracted much attention due to its negative impact on public health worldwide. Indeed, common environmental toxicants such as heavy metals (e.g. cadmium), metalloids (e.g. arsenic), and organic xenobiotics (e.g. benzo[a]pyrene, TCDD) are established potentiators of solar UV damage and skin carcinogenesis (21–23). Co-carcinogenicity of various exposome factors potentiating solar UV-induced skin photocarcinogenicity is firmly documented, as applicable to: (*i*) pollutants such as polyaromatic hydrocarbons including benz[a] pyrene (from cigarette smoke and combustion engines), (*ii*) arsenic (from drinking water), (*iii*) hypercaloric dietary intake/metabolic dysregulation, (*iv*) molecular therapeutics [acting as photo sensitizers or immunosuppressants], (*v*) and microbial infection (HPV, Merkel cell polyoma virus, Malassezia spp.) (21–28). To the contrary, dietary intake of specific phytochemicals representing an extrinsic exposome-related factor might enhance skin barrier function and antagonize photo-carcinogenesis, acting through modulation of specific molecular pathways associated with enhancement of antioxidant stress response (with involvement of the Keap1/NRF2 pathway) and suppression of inflammatory signaling (NFκB and AP-1) (9, 29).

Likewise, impairment of skin barrier function and health can result from the overlap of extrinsic (exposome-related) and intrinsic factors that interact and potentially synergize in complex ways. For example, it is well documented that smoking (an external exposomal factor) accelerates skin aging (intrinsic factor) (30). Likewise, human skin photoaging represents the overlap of intrinsic factors (such as cellular senescence as a function of chronological age) and structural/functional alterations due to environmental solar exposure (31). In the context of co-carcinogenicity, it has long been known that intrinsic genetic alterations that impair DNA repair capacity are associated with an increased UV-induced skin cancer incidence as substantiated paradigmatically by xeroderma pigmentosum patients with excision repair deficiencies underlying a pronounced increase in skin cancer risk (32, 33).

Abbreviations: HOCl, Hypochlorous acid; UV, Ultraviolet; CPDs, Cyclobutane pyrimidine dimers; ROS, Reactive oxygen species; SABV, Sex as a biological variable; MPO, Myeloperoxidase; CBPs, Chlorination byproducts; CSAD, Cysteine sulfinic acid decarboxylase; CDO1, Cysteine dioxygenase; FIFRA, Federal Insecticide, Fungicide, and Rodenticide Act; DBP, Disinfection byproducts; PPCPs, Pharmaceuticals and personal care products; AHR, Airway hyperresponsiveness; GI, Gastrointestinal.

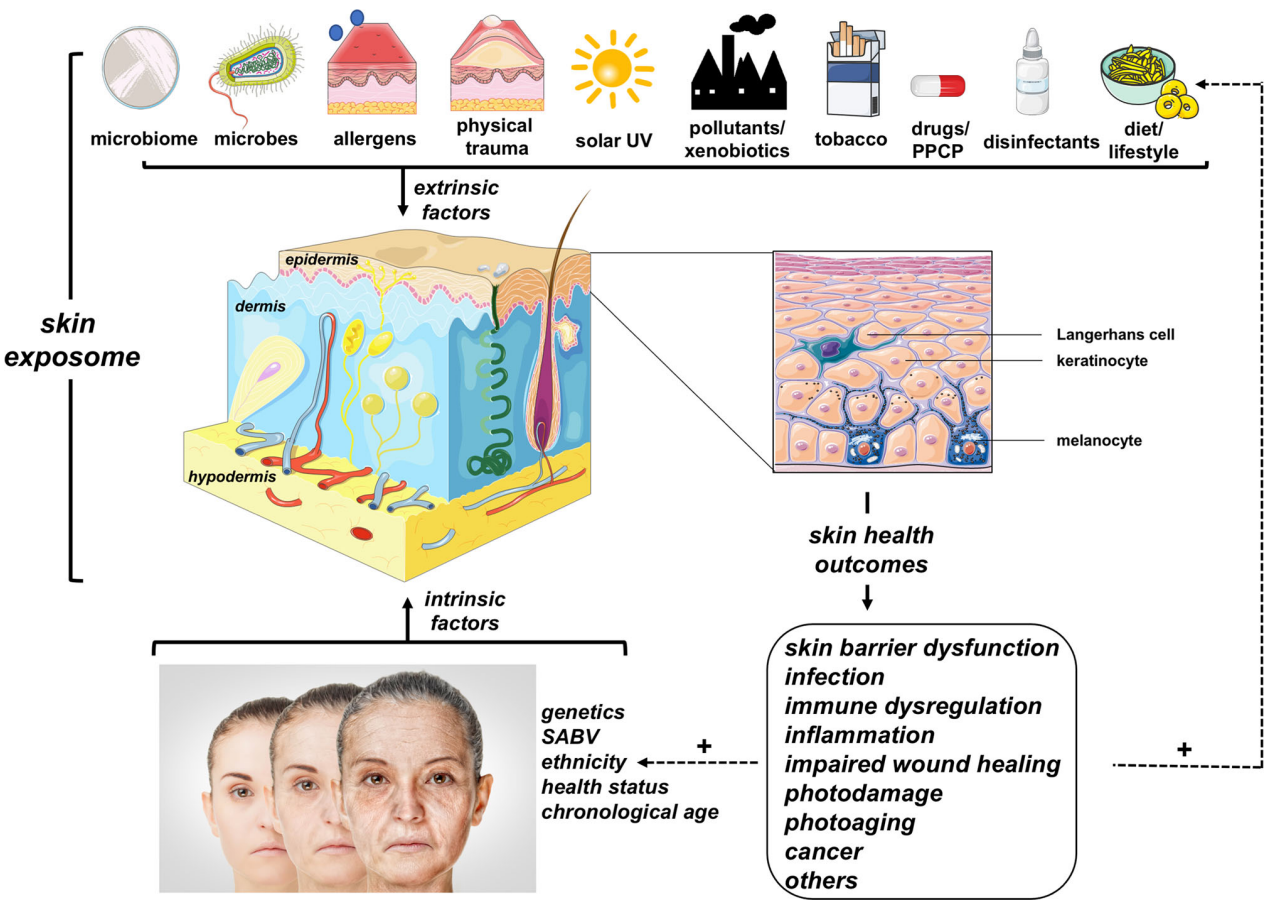

FIGURE 1 | The Skin Exposome. A multitude of extrinsic environmental factors (referred to in their entirety as the 'skin exposome') impact structure and function of skin and its corresponding cellular components. The complex (i.e. additive, antagonistic, or synergistic) interactions between multiple extrinsic (exposome) and intrinsic (biological) factors are important determinants of skin health outcomes. Unfolding skin pathology can potentiate (+) the cutaneous vulnerability to further environmental exposures or intrinsic factors (fueling a positive feedback loop). (PPCP, pharmaceuticals and personal care products; SABV, sex as a biological variable). Image was created using free imaging software: smart.servier.com.

Recently, hypochlorous acid (HOCl) has been identified as an environmental toxicant relevant to cutaneous exposures (34–36). Here, given the ubiquitous use of topical HOCl-based disinfection strategies combined with its established biological role as an essential determinant of neutrophil-related innate immunity, we review the role of this powerful electrophile as an understudied chemical component of the skin exposome with special emphasis on novel data that substantiate HOCl-dependent modulation of solar UV-induced skin carcinogenesis.

HYPOCHLOROUS ACID AND ITS CONJUGATED ANION: INNATE AND ENVIRONMENTAL MEDIATORS OF OXIDANT CHLORINATION STRESS

HOCl in Innate Immunity

Basic physicochemical properties of HOCl are relevant to its endogenous physiological function including its role as an innate immune factor, topical antimicrobial, and environmental toxicant (**Figure 2**) (37, 38).

Importantly, multiple chemical parameters dictate the biological function of HOCl serving as an important component of the skin exposome. In this context it should also be mentioned that HOCl-dependent chlorination stress is dictated by both thermodynamic and kinetic parameters that ultimately determine susceptibility of various biochemical targets (39–43).

First, HOCl is (*i*) a weak acid, (*ii*) a powerful chlorination agent, and (*iii*) direct- or indirect-acting oxidant. HOCl contains one labile proton (pKa = 7.46) dictating the co-existence between acid and conjugated base under physiological conditions at near equimolar ratio (**Figure 2A**). Another important physico-chemical feature of HOCl and its corresponding anion [OCl^- (hypochlorite)], relevant to environmental co-exposure scenarios, is its ability to absorb solar UVB (290-320 nm) photons and, as a consequence, undergo photolysis (**Figure 2B**). HOCl maximally absorbs at 237 nm and 289 nm

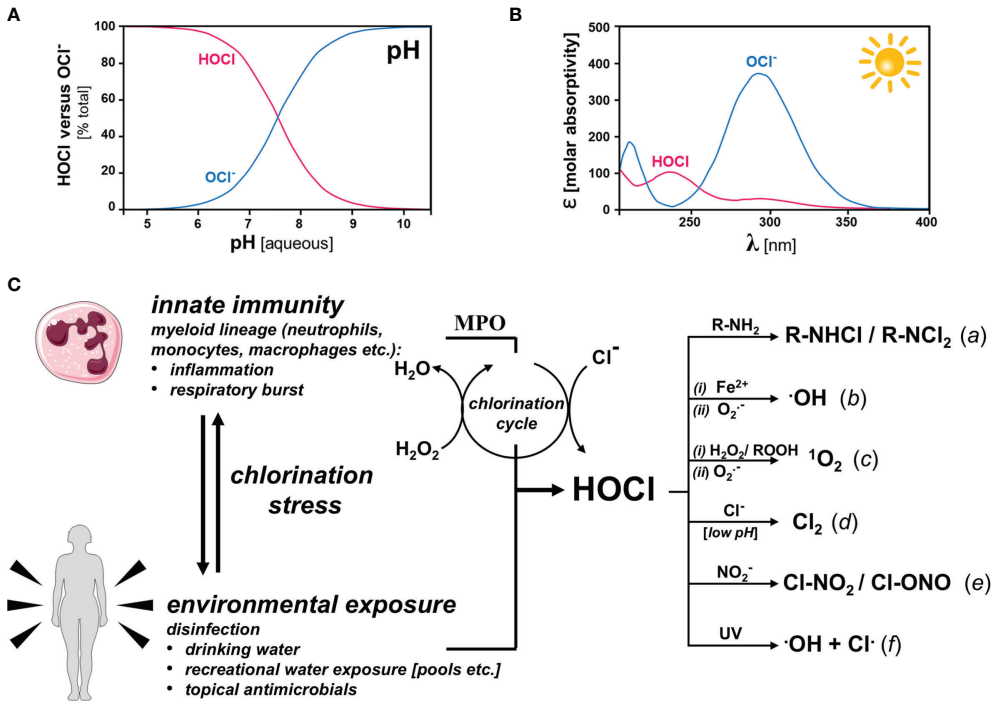

FIGURE 2 | HOCl/OCl-: Physicochemical Properties, Innate and Environmental Origin, and Formation of HOCl-Derived Secondary Oxidants Under Physiological Conditions (**A**) pH-dependent speciation (HOCl versus OCl-). At physiological pH, HOCl and OCl- occur at near equimolar ratios **(B)** Photon Absorptivity. HOCl and its corresponding anion differ with regard to photo-absorptive properties: HOCl (λ_{max} = 235 nm; ϵ = 101); OCl^- (λ_{max} = 292 nm; ϵ = 365). OCl^- absorptivity covers the solar UVB (290-320 nm) and UVA-II (320-340 nm) regions. **(C)** Biological and environmental sources of HOCl formation and HOCl-derived secondary oxidants. Left panel: Innate immune activation causes HOCl production by specific myeloid cells under conditions of inflammation and respiratory burst *via* the myeloperoxidase (MPO)-catalyzed chlorination cycle that consumes H_2O_2 for Cl^- oxidation. Environmental exposure to HOCl occurs in the context of freshwater disinfection (e.g. drinking water, recreational use, etc.) and topical antimicrobial intervention. Right panel: HOCl-derived secondary oxidants. Apart from acting as potent oxidizing species, HOCl/OCl^- may be involved in a number of biochemically relevant reactions producing secondary oxidants including: (*a*) chloramine formation; (*b*) hydroxyl radical formation downstream of (*i*) Fe(II)-dependent Fenton or (*ii*) superoxide chemistry; (*c*) singlet oxygen formation downstream of (*i*) peroxide or (*ii*) superoxide chemistry; (*d*) molecular chlorine formation with involvement of Cl^- at low pH; (*e*) formation of nitryl chloride and chlorine nitrite upon reaction with nitrite; and (*f*) formation of hydroxyl and chlorine radicals as a result of UV-driven photolysis.

with molar extinction coefficients of 102 and 36.1, respectively; OCl^- maximally absorbs at 292 nm with a molar extinction coefficient of 378. Consequently, photolysis of HOCl by environmentally relevant UVB is a function of pH. Indeed, environmental UV exposure might cause photolysis reactions with formation of various reactive species including the hydroxyl and chlorine free radicals, among others. However, the specific role of photolysis in the mediation of biological HOCl-based chlorination stress remains to be explored, given the opposing effects of a short reactivity-limited lifetime and sustained HOCl-release from photostable organic precursors including chloramines (such as the swimming pool disinfectant trichloroisocyanuric acid; see **Figure 5A**, structure 5) (44, 45).

Remarkably, HOCl, a weak halogen-based acid and powerful oxidant, serves two seemingly unrelated molecular roles: (*i*) as an innate immune factor [acting as a myeloperoxidase (MPO)-derived microbicidal factor] and (*ii*) as a chemical disinfectant used in freshwater processing, both in the context of drinking water safety and recreational use (e.g. swimming pool/hot tub disinfection) (37, 38). Importantly, HOCl and its conjugated base represent a potent oxidizing redox system [$E^{0'}$ = +0.9 (OCl^-); $E^{0'}$ = +1.48 V (HOCl)] under physiological conditions. In this context, it is important to notice that the major anti-microbially active species is thought to be HOCl (compared to the hypochlorite anion), consistent with the half-cell oxidation-reduction potentials and an increased ability of the uncharged HOCl species to penetrate cell walls and membranes of pathogens. Involvement of MPO in antimicrobial response and host pathogen interaction have been covered elsewhere and will not be the topic of this review (46). The potent oxidant HOCl/OCl^- serves as an endogenous microbicidal agent, generated by myeloid lineage-derived effector cells (including neutrophils). Indeed, during the respiratory burst, MPO-dependent oxidation of chloride anions (using NADPH oxidase-derived superoxide/hydrogen peroxide) produces HOCl and other hypohalous acids such as HOBr (hypobromous acid), HOI (hypoiodous acid), and HOSCN (hypothiocyanous acid)] as an essential component of antimicrobial innate immunity (**Figure 2C**) (47, 48). The 'chlorination cycle' catalyzed by MPO involves the hydrogen peroxide-dependent oxidation of reactive site ferric iron [Fe

(III)] forming a highly reactive oxy-ferryl [Fe(IV)=O] radical cation capable of oxidizing chloride anions leading to the formation of HOCl and regeneration of the ferric iron MPO. Importantly, endogenous hypohalous acids, even though serving innate host defense functions, may also induce tissue damage at sites of inflammation, an area of active research in the context of neurodegenerative disease (M. Alzheimer; M. Parkinson), metabolic and cardiovascular dysfunction (atherosclerosis; diabetes), autoimmune dysregulation, cancer, and chronological aging, among others (47, 49, 50). Importantly, beyond a role in cutaneous innate immunity, the MPO system has also been involved in various skin pathologies, either serving as a causative factor or biomarker in inflammation, contact hypersensitivity and irritation, psoriasis, UV-damage, photoaging, and carcinogenesis (51–59).

HOCl in Freshwater Disinfection: From Human Consumption to Recreational Use

The disinfection of drinking water supply by HOCl-dependent chlorination may well be regarded as the most important public health milestone in human history. Among the sustainable development goals adopted by members of the United Nations in 2015 is goal 6, which aims to provide all people with equal access to safe and affordable drinking water, sanitation and hygiene as consistent with the 2010 proclamation of the general assembly that such encompasses a human right. Despite substantial progress, it is currently estimated that more than 2 billion people lack access to safely managed drinking water and basic hygiene, while nearly half of the human population lacks sanitation. Indeed, according to global population projections and climate change models, supply problems surrounding safe water will be of utmost importance for this century. Considering these trends, continual optimization of the methods for drinking water sanitation, distribution, safe storage and wastewater treatment will be necessary to reduce water related health disparities on a global scale (60).

HOCl-Based Swimming Pool Disinfectants: Oxidative Potentiators of Cutaneous Solar UV Damage as an Unexplored Environmental Exposure of Global Importance

HOCl is the active microbicidal principle released by standard swimming pool disinfectants employed abundantly worldwide. According to CDC, there are 10.4 million residential and 309,000 public swimming pools and over 7.3 million hot tubs in the United States alone (https://www.cdc.gov/healthywater/swimming/fast-facts.html). Even though HOCl, commonly referred to as 'swimming pool chlorine', is the most frequently used halogen-based oxidizing pool disinfectant, little research has addressed toxicological implications and damage potentiation resulting from combined exposure to HOCl-based swimming pool disinfectants and solar UV as it occurs on a global scale in the context of recreational swimming pool use (34). Pool disinfection is an essential barrier to the spread of germs. To ensure a non-infectious healthy pool environment, operators try to maintain a desired range (1.0-1.5 ppm free HOCl; for outdoor swimming pools and indoor pools smaller than 20 m^2, the recommended maximum level is 5 ppm). In recent years, use of sodium dichloroisocyanurate, an organic HOCl-precursor, has gained frequent use, but HOCl/OCl^- is the predominantly active microbicidal agent (34, 61).

Human skin is extensively exposed to HOCl-based pool disinfectants causing oxidation and chlorination of specific molecular targets; however, little molecular research exploring the potentially adverse cutaneous and systemic effects resulting from exposure to HOCl-disinfectants during recreational swimming pool use has been conducted. Given the important role of photo-oxidative mechanisms underlying adverse cutaneous effects of solar UV exposure and the largely oxidative nature of chlorination-induced damage, it seems reasonable to expect synergistic molecular interactions that drive HOCl-potentiation of sun damage in exposed individuals. Indeed, according to the recent *WHO Guidelines for Safe Recreational Water Environments*, epidemiological evidence indicates that risk of sunburn and cutaneous photodamage is increased in swimming pool environments.

In addition to direct target chlorination and oxidation, HOCl-dependent reactions of biological relevance in inflammation and antimicrobial defense (-also observed in the context of topical disinfectant use-), might be mediated through the formation of numerous HOCl-derived electrophilic species (**Figure 2C**; right portion). Chloramine formation involves the HOCl-dependent derivatization of primary and secondary biological amines as contained in small biochemicals (such as histamine and taurine) and macromolecules (proteins etc.) (62–64). Moreover, hydroxyl radical formation may occur downstream of either Fe(II)-dependent Fenton chemistry, scenarios observable under conditions of MPO-facilitated heme degradation as a consequence of excess HOCl formation or pathological elevation of labile iron (65–67). Likewise, hydroxyl radicals can form upon reaction of HOCl with superoxide free radicals (68). Interestingly, HOCl-dependent formation of highly reactive photoexcited molecular oxygen [$^1O_2$ (singlet oxygen)] has been documented without mechanistic involvement of photons downstream of peroxide (including linoleic acid hydroperoxide), superoxide, or chloramine chemistry involving the chemical formation of photo-excited states (commonly referred to as 'chemiexcitation') (69–71). Molecular chlorine (Cl_2) is another species formed downstream of MPO-dependent transformation of Cl^- anions and hydrogen peroxide at low pH, relevant to cholesterol chlorination in atherosclerotic pathology (72–74). Furthermore, upon reaction with nitrite, formation of nitryl chloride and chlorine nitrite might occur, reactions relevant to inflammatory protein nitration (75). Lastly, as a result of UV-driven photolysis generation of hydroxyl and chlorine radicals has been documented, a reaction of potential relevance to environmental co-exposure scenarios where solar photons in the UVB range might cause HOCl/OCl^- degradation with formation of reactive free radical species consistent with the extensive UVB absorptivity of OCl^- (38).

BIOMOLECULAR TARGETS OF CHLORINATION STRESS: FROM CHEMICAL MODIFICATION TO PATHOPHYSIOLOGICAL CONSEQUENCES

Chlorination stress that occurs under physiological or environmental exposure-relevant conditions impacts structure and function of numerous classes of biomolecules, either through covalent introduction of chlorine (and chlorine-derived substituents) or through indirect oxidative insult. HOCl, in equilibrium at physiological pH with its anionic form [hypochlorite (OCl^-)], may also induce tissue damage at sites of inflammation involving the oxidation and chlorination of biomolecules targeting peptides (e.g. glutathione), proteins, lipids, and nucleic acids (39, 42, 43, 47, 76, 77).

Previous research has identified key molecular modifications downstream of chlorination stress targeting amino acids, peptides, and proteins as dominant targets of biologically-relevant chlorination stress (**Figure 3A**). For illustration, a hypothetical heptapeptide [H_2N-Tyr-Trp-His-Lys-Met-Cys-Arg-COOH] has been envisioned that exemplifies the range of possible amino acid modifications induced by HOCl exposure including dichloro-tyrosine, hydroxy-tryptophan, histidine chloramine, lysine mono- or dichloramine, methionine sulfoxide, cysteine sulfenic/sulfinic/sulfonic acid, and arginine chloramine (78). Protein chlorination has been associated with structural changes of target proteins including fragmentation, crosslinking, aggregation, unfolding, and modulation of specific functions such as immunogenicity, enzymatic activity and ligand-receptor interaction (48, 79). Numerous proteins are subject to chlorination stress-induced modulation through chemical changes under physiological conditions, including plasma proteins [e.g. HSA, alpha2M], histones, heat shock/ER stress response mediators and calcium signaling components (e.g. GRP78, SERCA), inflammatory signaling molecules (e.g. IL-6, IKK) and mediators of tissue remodeling (e.g. MMP7, TIMP-1), causing effects that are mostly consistent with modulation, attenuation, and resolution of inflammatory tissue responses (35, 80–89). Specifically, inactivation of IKK (inhibitor of IκB kinase) through oxidation (Cys114/115) is thought to cause the hypochlorite-dependent attenuation of psoriasis observable upon topical application (35). Similarly, GRP78 (glucose-regulated protein 78, HSPA5) modification through chloramine adduction (Lys 353) has been suggested to modulate autophagy and apoptosis in A549 lung cancer cells, and N-chlorination of HSA (human serum albumin) converts plasma proteins into efficient activators of the phagocytic respiratory burst (46, 86). In addition, biogenic amines, mostly through chloramine formation, have been demonstrated to serve as biomolecular targets of chlorination stress including histamine, serotonin, melatonin, and taurine among others (90, 91).

Consistent with chlorination-associated electrophilic stress, unsaturated lipids serve as major HOCl-targets under physiological conditions (**Figure 3B**) (92–99). Indeed, free fatty acids, triglycerides, phospholipids, as well as cholesterol and its derivatives, have all been validated as being susceptible to chemical modification under conditions of physiological or environmental chlorination stress conditions (**Figure 3B**). For example, HOCl-mediated modification of cholesterol forms a number of cholesterol-chlorohydrin stereoisomers as depicted; in addition, phospholipids may undergo derivatization at nitrogen-containing head groups (forming the respective chloramine) or at sites of unsaturation, followed by further oxidation/decarboxylation and N-centered free radical formation. In addition, other biochemical lipid mediators including plasmalogens, prostaglandins, and leucotrienes, involved in tissue remodeling and inflammatory signaling, have been shown to be subject to HOCl-dependent adduction with consequent alteration of signaling properties (98).

Nucleic acids are important targets of chlorination stress with possible mutagenic, genotoxic, and cytotoxic outcomes downstream of chemical modification (**Figure 3C**) (39, 100–102). Specifically, it is well documented that HOCl exposure causes chemical modification of DNA and RNA (and their respective nucleotides, nucleoside, and free nucleobases, irrespective of ribose- or deoxyribose- substitution). For example, HOCl-modification of deoxyadenosine forms 8-chlorodeoxyadenosine, and HOCl-modification of deoxyguanosine forms 8-chlorodeoxyguanosine. Interestingly, HOCl-modification of deoxycytidine forms a 5-chlorodeoxycytidine-intermediate, followed by spontaneous deamination forming stable 5-chlorodeoxyuridine causing miscoding damage downstream of chlorination stress. Indeed, chloro-derivatives of nucleic acids and their constitutive bases, apart from their functional involvement in mutagenic events, may also play an important yet underappreciated role as biomarkers of chlorination stress characteristic of specific pathological conditions.

ENDOGENOUS, PHYTOCHEMICAL, AND SYNTHETIC HOCL-ANTAGONISTS: ANTIOXIDANTS AND QUENCHERS

Numerous molecular entities of endogenous or phytochemical origin have been shown to antagonize chlorination stress that occurs as a consequence of exposure to HOCl including amino acid derivatives (taurine, glutathione, serotonin, serotonin, carnosine, ovothiol, ergothioneine), phenolics (gallic acid, nordihydroguaiaretic acid, quercetin), and B_6 vitamers (pyridoxal, pyridoxine, and pridoxamine), attributed mostly to chemical reactivity (i.e. sacrificial quenching) (**Figure 4A**). In addition, antagonists of MPO enzymatic activity (such as the synthetic MPO inhibitor verdiperstat or the endogenous metabolite uric acid) blocking HOCl formation have been explored for pharmacological control of pathophysiological chlorination stress (47, 62, 91, 103–109).

Among these biomolecules, B_6-vitamers deserve special recognition since they have been shown to exert protection against chlorination stress as assessed using *in vivo* disease models, an effect attributed to formation of stabilized chloramine derivatives (110). Likewise, imidazole-derivatives

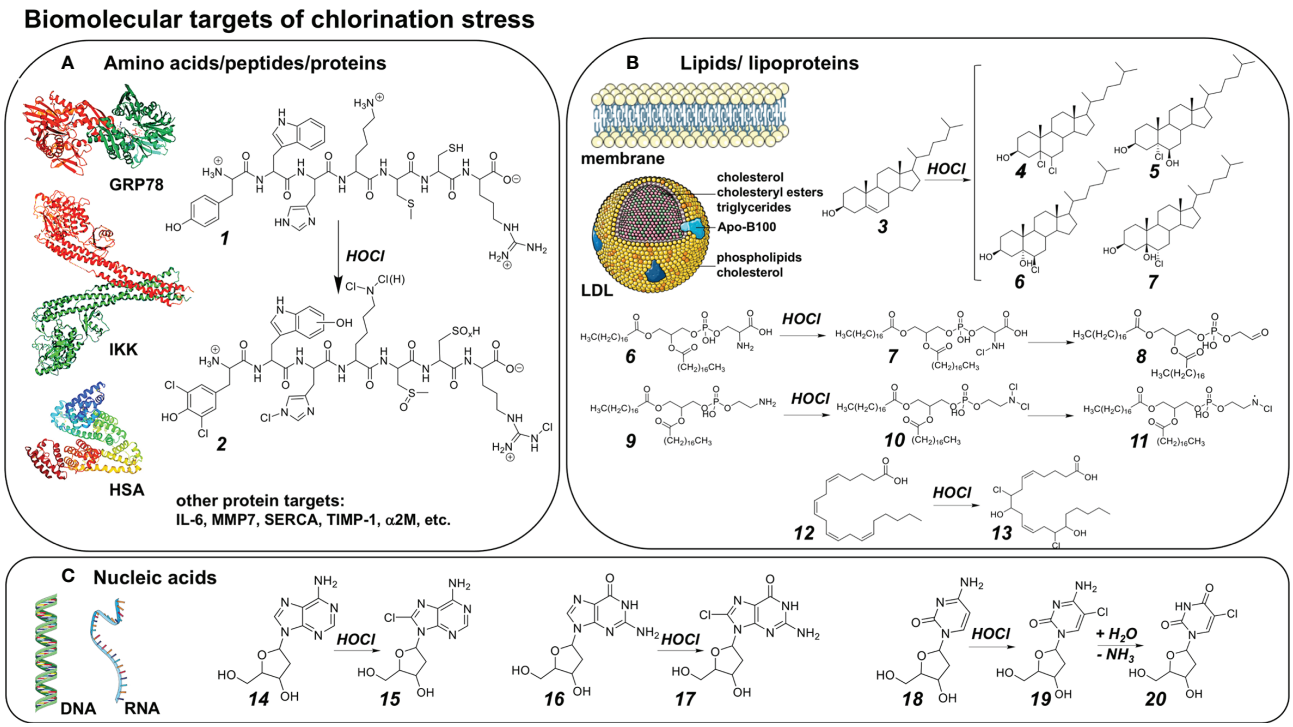

FIGURE 3 | Biomolecular Targets of Chlorination Stress **(A)** Amino acids, peptides, and protein targets of chlorination stress. Theoretical heptapeptide [H_2N-Tyr-Trp-His-Lys-Met-Cys-Arg-COOH (1)] illustrating the range of possible amino acid modifications (2) induced by HOCl (from amino- to carboxyterminus): Dichloro-tyrosine, hydroxy-tryptophan, histidine chloramine, lysine mono- or dichloramine, methionine sulfoxide, cysteine sulfenic/sulfinic/sulfonic acid, arginine chloramine. **(B)** Fatty acids, lipids, and lipoproteins as targets of chlorination stress. HOCl-mediated modification of cholesterol (3) forms a number of cholesterol chlorohydrin stereoisomers: 5,6-dichloro cholesterol (4); (5R,6R)-5-chloro-6-hydroxy cholesterol (5); (5R,6R)-6-chloro-5-hydroxy cholesterol (6); (5S,6S)-6-chloro-5-hydroxy cholesterol (7), among others. For phospholipids, HOCl may either exert its effects near the head group, or at sites of unsaturation: HOCl-mediated modification of phosphatidylserine (6) results in phosphatidylserine chloramine (7), with further oxidation/decarboxylation to phosphatidyl glycoaldehyde (8). HOCl-mediated modification of phosphatidylethanolamine (9) results in the respective dichloramine (10) subsequently forming N-centered radicals acting as long-lived mediators. For simplicity, for both phospholipids each lipid moiety is stearate. Fatty acids possessing greater degrees of unsaturation are more prone to modification by HOCl: HOCl-mediated modification of arachidonic acid (12) results in the formation of arachidonic acid chlorhydrins such as 8,14-dichloro-9,15 dihydroxy arachidonic acid bis-chlorohydrin (13). **(C)** Nucleic acids as targets of chlorination stress. HOCl may modify DNA, RNA, and free nucleobases. (For simplicity, only HOCl-mediated modification of deoxyribosides is shown.) HOCl-modification of deoxyadenosine (14) forms 8-chlorodeoxyadenosine (15). HOCl-modification of deoxyguanosine (16) forms 8-chlorodeoxyguanosine (17). HOCl-modification of deoxycytidine (18) forms 5-chlorodeoxycytidine (19), followed by spontaneous deamination forming 5-chlorodeoxyuridine (20).

(e.g. L-histidine, carnosine, carcinine) and thio-imidazole-derivatives (ergothioneine and sea urchin-derived ovothiol) have been identified as potent chlorination stress inhibitors (111–113).

Moreover, the cysteine-derived metabolite taurine (2-amino-ethane-sulfonic acid) has now been identified as a major endogenous HOCl-directed scavenger and antioxidant, attenuating physiologically relevant chlorination stress (**Figure 4B**). Strikingly, neutrophils represent a large reservoir of free taurine compromising approximately 50% of the cellular amino acid/amino acid-derivative pool thought to be involved in direct chemical protection against cytotoxic consequences of the respiratory burst associated with microbicidal HOCl formation (114). Taurine formation occurs as the result of enzyme-catalyzed cysteine transformation through intermediate generation of L-cysteine sulfinic acid and hypotaurine (**Figure 4B**). The consequent formation of N-chlorotaurine, representing a chlorinated adduct with attenuated reactivity, has also been interpreted as an intermediate step facilitating the extension of the phagocytic activity range, enabling enhanced stability and diffusion, spatially amplifying the range of oxidative antimicrobial effects. Indeed, attenuated chlorination reactivity of N-Chlorotaurine has been attributed to sulfonic acid-dependent electrostatic anionic shielding of the adjacent chloramine function that is amenable to chloro-transfer if attacked by biomolecular nucleophiles (115).

Importantly, N-chlorotaurine formation may cause the negative regulation of inflammatory processes by multiple distinct molecular mechanisms attenuating NF-kB and related cytokine signaling (88, 116). Interestingly, taurine might not only attenuate direct chemical reactivity of HOCl through sacrificial quenching, but chloro-taurine may then act as a redox-directed signaling modulator of major inflammatory targets and pathways. Indeed, it has been shown that N-chlorotaurine modulates inflammatory pathologies attributed to chemical

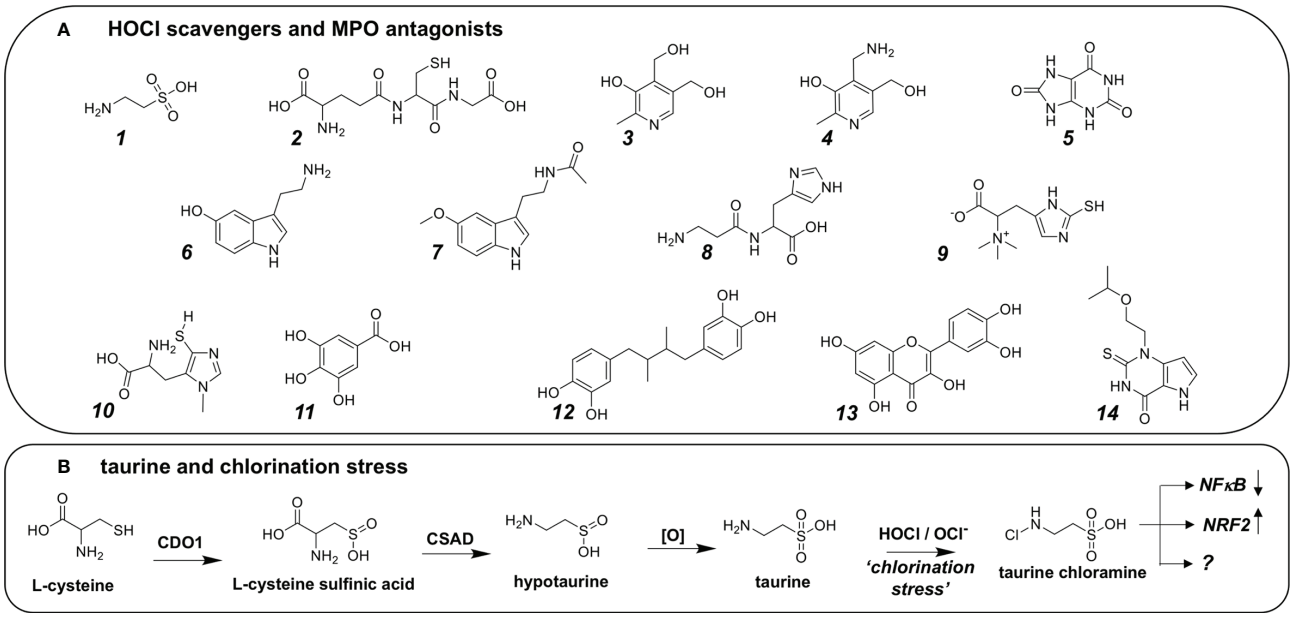

FIGURE 4 | Biochemical, Natural Product, and Synthetic HocI Scavengers and MPO Antagonists. **(A)** Endogenous chemical entities: 1. Taurine, 2. Glutathione, vitamins: 3. Vitamin B_6, 4. Pyridoxamine; neurotransmitters: 6. Serotonin, 7. Melatonin 8. Carnosine; 9. Ergothioneine. Natural products: 10. Ovothiol, 11. Gallic acid, 12. Nordihydroguaiaretic acid, 13. Quercetin. Endogenous and synthetic MPO antagonists: 5. Uric acid, 7. Melatonin, 14. AZD3241 (Verdiperstat). **(B)** Endogenous production of taurine as a possible sink for HOCl. First, L-cysteine is oxidized by cysteine dioxygenase (CDO1) to form L-cysteine sulfinic acid, which in turn is decarboxylated by the enzyme cysteine sulfinic acid decarboxylase (CSAD) forming hypotaurine. Hypotaurine may undergo spontaneous oxidation to form taurine, acting as a sacrificial quencher of HOCl/OCl^- forming taurine chloramine as a moderately active chloramine with attenuated chlorination reactivity. Interestingly, taurine chloramine has been demonstrated to exert control over downstream signaling pathways including downregulation of NFκB, and upregulation of KEAP1-NRF2. As such, it has been hypothesized that taurine chloramine acts through posttranslational modification of distinct amino acid residues on transcription factors, among other effects.

modification of inflammatory factors, such as IL-6 and NFkB. Indeed, N-chlorotaurine exposure of IL-6 causes oxidation of residues relevant to IL6R receptor-binding (Met161 and Trp157) (88). Negative modulation of NF-κB by N-chlorotaurine (and other chloramines such as glycine chloramine) is thought to originate from oxidation of Met45 in IκB (preventing its ubiquitination and proteasomal degradation) (116, 117). Importantly, NRF2, the master transcriptional regulator of cellular antioxidant responses, has also been shown to be responsive to N-chlorotaurine-mediated chlorination stress, an effect attributed to electrophilic adduction and inactivation of Keap-1, the redox-sensitive negative regulator of this transcription factor (118).

MOLECULAR MEDIATORS, SIGNALING PATHWAYS, AND HUMAN TARGET ORGANS OF CHLORINATION STRESS

Molecular chlorination stress relevant to human health originates from HOCl (among other endogenous hypohalous acids including HOI and HOBr, formed mostly in the context of innate immunity) and is complemented by exposure to HOCl (and related derivatives) originating from exogenous sources. Specifically, environmental exposure-relevant chlorination agents include hypochlorous acid (and its corresponding anion) as well as diverse chloramines (e.g. monochloramine, dichloramine, nitrogen trichloride, chlorinated isocyanuric acid-derivatives) formed as a result of freshwater chlorination (**Figure 5A**) (119, 120). Interestingly, trichloroisocyanuric acid as well as its di-chloro-analogue are EPA-approved under FIFRA (Federal Insecticide, Fungicide, and Rodenticide Act) regulations, used globally for drinking water and freshwater disinfection (such as in swimming pools), offering increased photostability and sustained HOCl release (44, 121). Importantly, chlorination byproducts (CBPs) including organohaloacetic acids and trihalomethanes (formed due to the presence of dissolved organic matter) and chlorite are subject to strict EPA regulation due to potential adverse health effects (122, 123). Strikingly, out of more than six hundred halogenation byproducts identified as of to date, only eleven are currently subject to strict EPA regulation (124). For example, mutagen X (3-chloro-4-(dichloromethyl)-5-hydroxy-5*H*-furan-2-one) is a disinfection byproduct derived from humic acids, not regulated by EPA, with suspected involvement in cancer risk elevation associated with consumption of chlorinated drinking water, an effect attributed to genotoxicity surpassing that of currently regulated CBPs

(including chloroform and bromodichloromethane) (125). Additionally, PPCPs introduced into the water supply are subject to HOCl-mediated chlorination and subsequent formation of CBPs. For example, common drugs including metformin, diclofenac, and tamoxifen entering freshwater sources are subject to direct chlorination causing drinking water contamination associated with largely unexplored implications for human health (126–129). Likewise, chlorination of PPCPs including sunscreen ingredients such as the common UVA-sunscreen avobenzone are associated with formation of a dichloro-species, and cosmetics are equally subject to chlorination with unexplored effects on human health (16, 130–135).

Human Target Organs of Environmental Chlorination Stress

Importantly, human organ dysfunction may occur as a result of chlorination stress originating from exogenous (environmental) and endogenous (innate) sources (47, 49). Indeed, these pathophysiological outcomes have been attributed to the molecular consequences of chlorination stress (mediated through HOCl/OCl^- and HOCl-derived organic chloramines) impacting genotoxic, proteotoxic, inflammatory, and redox stress responses involving modulation of crucial transcription factor systems including p53, Keap1/NRF2, HSF1, IKK/NFκB, and AP-1 (**Figure 5B**) (35, 36, 118, 136–138). Likewise, signaling cascades including MAPKs (p38, ERK1/2) are sensitive to HOCl exposure attributed in part to tyrosine phosphatase modulation through cysteine-oxidation (139, 140). Also, in the context of balancing HOCl-related organ toxicity and therapeutic effects, it should be mentioned that the indiscriminate HOCl-dependent induction of chlorination stress might be associated with adverse irritant effects (51, 141–144).

Here, we will briefly focus on organ-specific toxicity of environmental exposure-induced chlorination stress (**Figure 5C**). In the lung, exposure to chlorination stressors has long been associated with a role in chronic inflammatory diseases of the respiratory system (137, 144–148). For example, competitive swimmers have been shown to suffer from high rates of asthma and airway hyperresponsiveness attributed to HOCl and volative DBP exposure (149, 150). In the context of pulmonary exposure, it is noteworthy that inhalational HOCl formulations are now undergoing clinical trials for prophylaxis and treatment of COVID-related respiratory infectious illness (*ClinicalTrials.gov Identifier: NCT04684550*). Moreover, there are concerns that innate or environmental chlorination stress might be related to the occurrence of lung malignancy related to genotoxic effects (86, 151, 152). Likewise, in the gastrointestinal tract, chlorination-associated changes have been substantiated, potentially impacting microbiome and barrier function, occurrence and severity of inflammatory pathology, and malignant progression (153–157). Hepatic toxicity related to chlorination stress, particularly in the context of environmental exposure to chlorination byproducts, has been documented extensively. Hepatic metabolism, biotransformation of drugs and xenobiotics have been investigated, and liver injury as well as malignancy have been substantiated as pathological outcomes resulting from chronic and dysregulated chlorination stress that might be potentiated by synergistic co-exposure involving multiple chlorinated chemical entities (158–161). Nephrotoxity and urogenital tract dysfunction are established pathological outcomes of chlorination stress. Among other pathologies, acute kidney injury, glomerulonephritis, diabetic nephropathy, and bladder cancer have been associated with exposure to pathological chlorination stress (110, 162–166).

Potential Therapeutic and Chemopreventive Opportunities of Topical HOCl With a Focus on Solar UV-Induced Skin Carcinogenesis

Remarkably, in addition to endogenous and environmental sources, skin HOCl exposure also occurs through application of topical disinfectants employed worldwide as clinical and consumer products (167–171). In human skin (as a function of concentration, pH, and exposure time), irritation and disruption of barrier function, alteration of the commensal microbiome, allergy, and contact hypersensitivity are expected outcomes of inappropriate topical HOCl product use not compliant with standard of care (**Figure 5D**) (142, 143). Also, it has been hypothesized that DBPs in drinking water correlate with risk of skin cancer (172). Importantly, HOCl-based therapeutics optimized for topical delivery are now serving as pharmaceutical formulations for wound management, scar prevention, diabetic ulcers, atopic dermatitis, pruritus, psoriasis, and seborrheic dermatitis (84, 168, 173, 174). Suppression of inflammatory gene expression with downregulation of iNOS and COX-2 downstream of HOCl-dependent IKK inactivation represents the crucial mechanistic basis underlying HOCl-dependent therapeutic efficacy targeting psoriasis and radiation dermatitis (35). The same mechanism has also been substantiated attenuating experimental melanoma progression as a result of myeloid cell-derived HOCl (175). In addition, HOCl-hydrogel formulations have shown immunotherapeutic efficacy against experimental murine melanoma (176). Consistent with these observations, a suppressive role of HOCl in the control of cancer cell viability and tumor progression has been envisioned and further substantiated (71, 177, 178).

More recently, we have investigated the molecular consequences of solar simulated ultraviolet (UV) radiation and HOCl combinations, a procedure mimicking co-exposure experienced for example by recreational swimmers exposed to both HOCl (pool disinfectant) and UV (solar radiation). First, we have profiled the HOCl-induced stress response in reconstructed human epidermis and SKH-1 hairless mouse skin (36). In AP-1 transgenic SKH-1 luciferase-reporter mice, topical HOCl suppressed UV-induced inflammatory signaling assessed by bioluminescent imaging and gene expression analysis documenting HOCl-antagonism of solar UV-induced AP-1 activation. Co-exposure studies (combining topical HOCl and UV) performed in SKH-1 hairless mouse skin revealed that the HOCl-induced cutaneous stress response blocks redox and

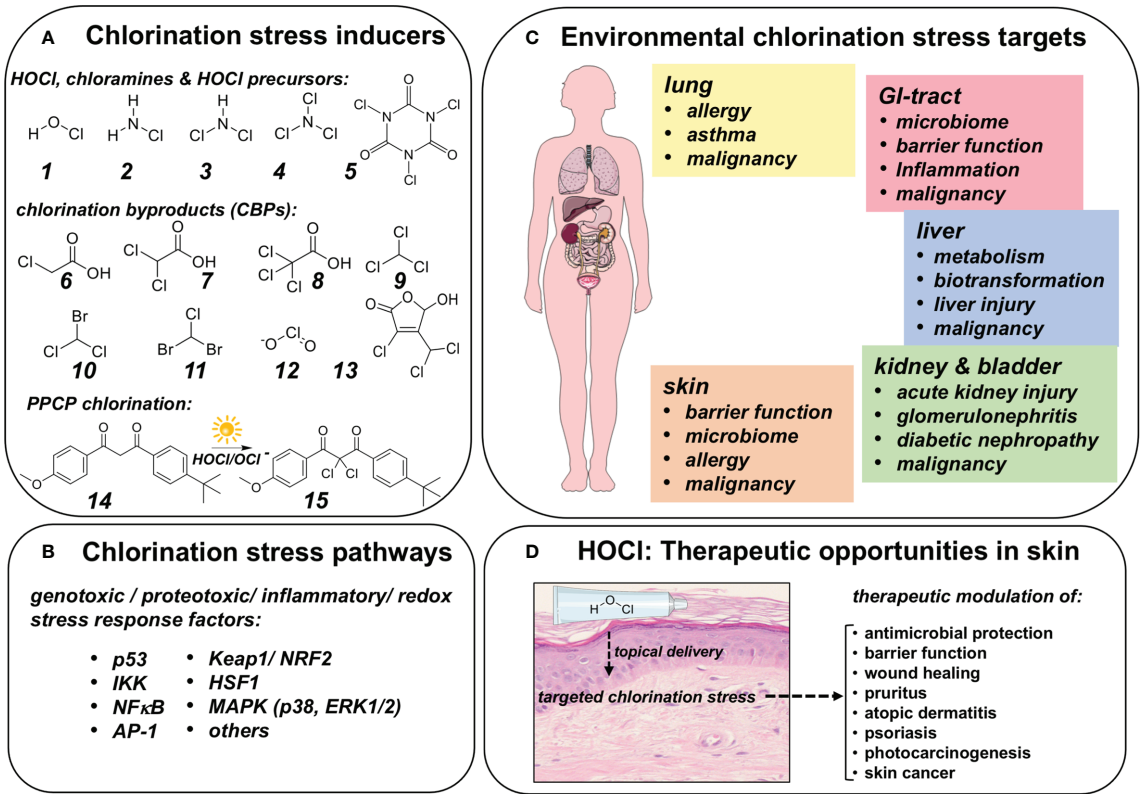

FIGURE 5 | Chlorination Stress: Molecular Inducers, Signaling Pathways, Human Target Organs and Therapeutic Opportunities In Skin. **(A)** Direct and indirect chlorination stress inducers. 1. Hypochlorous acid, 2. Monochloramine, 3. Dichloramine, 4. Nitrogen Trichloride, 5. Trichloroisocyanuric acid. Upon chlorination of fresh water, chlorination byproducts (CBPs) are formed due to the presence of dissolved organic matter: Haloacetic acids: 6. Chloroacetic acid, 7. Dichloroacetic acid, 8. Trichloroacetic acid; Trihalomethanes: 9. Trichloromethane, 10. Bromodichloromethane, 11. Chlorodibromomethane, 12. Chlorite, all of which are subject to governmental regulation. Remarkably, numerous major chlorinated byproducts remain largely unexplored (and unregulated) such 3-chloro-4-(dichloromethyl)-5-hydroxy-5*H*-furan-2-one (13, commonly referred to as 'mutagen X'). Additionally, pharmaceuticals and personal care products (PPCPs) introduced into the water supply are subject to HOCl mediated chlorination. As shown, the common UVA-sunscreen avobenzone (14) is chlorinated to produce a dichloro-species (15). **(B)** Chlorination stress signaling pathways. It has been demonstrated that chlorination stress may impact genotoxic, proteotoxic, inflammation and redox responses including p53, Keap1/NRF2, IKK/NFκB, and AP-1. **(C)** Human target organs of chlorination stress. Chlorination stress impacts multiple organ systems causing specific functional outcomes as discussed. **(D)** HOCl: Therapeutic opportunities in skin. HOCl may be used as a topical agent for therapeutic induction of chlorination stress in the context of antimicrobial intervention, impaired barrier function, wound healing, pruritus, atopic dermatitis, psoriasis, skin cancer, and prevention of photocarcinogenesis.

inflammatory gene expression elicited by subsequent acute solar UV exposure. Remarkably, in the SKH-1 high-risk mouse model of UV-induced human keratinocytic skin cancer, relevant to actinic keratosis and subsequent malignant progression, topical HOCl blocked tumorigenic progression and inflammatory gene expression (*Ptgs2*, *Il19*, *Tlr4*), confirmed by immunohistochemical analysis including 3-chloro-tyrosine-epitopes.

These data illuminate the molecular consequences of HOCl-exposure in cutaneous organotypic and murine models assessing inflammatory gene expression and modulation of UV-induced carcinogenesis. However, the specific mechanistic involvement of NFκB and AP-1 in the HOCl-induced attenuation of UV-induced skin inflammatory gene expression and carcinogenesis remains to be elucidated. With relevance to cancer-directed preventive and potentially therapeutic activity, an HOCl-induced increased immunogenicity of proteins and enhanced uptake by dendritic cells have been observed (179). Likewise, activity as a natural adjuvant (through induction of adaptive immunity by HOCl-dependent oxidation of N-linked carbohydrates in glycoprotein), subsequently enhancing scavenger receptor uptake by antigen presenting cells, has been demonstrated, linking HOCl-potentiation of innate and adaptive immunity (180).

If translatable to photodamaged human skin, these observations provide novel insights on molecular consequences of chlorination stress not only relevant to environmental exposure but indicative of a potential photo-chemopreventive utility for topical intervention targeting early (actinic keratosis) and advanced stages of nonmelanoma skin cancer.

FUTURE DIRECTIONS

Chlorination stress associated with $HOCl/OCl^-$ exposure originating from innate and environmental sources has now been identified as a double-edged molecular sword, mediating essential functions in the context of innate immunity towards microbial attack and exerting effects that are either detrimental or therapeutic to human health, particularly in the context of skin anti-inflammatory and cancer photochemopreventive topical intervention. Harnessing HOCl-dependent preventive and therapeutic effects that might benefit human patients will depend on the development of novel chemical entities and advanced formulations allowing a more controlled and targeted modulation of chlorination stress (70, 181). Indeed, additional research must carefully explore dose regimens and extended release formulations that achieve anti-inflammatory and photo-chemopreventive effects while avoiding potential HOCl-induced tissue damage and irritation. In the same way, availability of specific biocompatible molecular fluorescent probes with diagnostic utility *in vitro* and *in vivo* (allowing imaging and quantitative analysis of physiological and therapeutic chlorination stress conditions) will expand our understanding of these multi-faceted versatile biochemical actors and processes as key determinants of health and disease (182).

AUTHOR CONTRIBUTIONS

Manuscript preparation: JS, JJ, GW. Conceptualization of work: GW. All authors contributed to the article and approved the submitted version.

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