From Precancers to Skin Rejuvenation—A Review of the Wide Spectrum of Current Applications and Future Possibilities for Plasma Dermatology

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ABSTRACT: Cold plasma medicine is a quickly evolving field with great laboratory research backing and expanding clinical use. Because of the easy accessibility of skin, dermatology is uniquely positioned to be at the forefront of exploring new areas for plasma treatment. Dermatologists are already using cold plasma for ulcers and conducting trials to treat precancerous keratoses, warts, nail fungus, and acne. Based on our understanding of cold plasma principles, numerous other skin conditions may become the targets of successful cold plasma therapies. In this article, we review the concepts behind current dermatological uses of cold plasma, challenges specific to dermatology, and the possible future of expanding cold plasma use to treat skin diseases.

KEY WORDS: dermatology, nonthermal atmospheric plasma, cold plasma, treatment

I. INTRODUCTION

Nonthermal atmospheric pressure physical plasma (cold plasma) is a partly ionized gas, also known as the fourth state of matter. It interacts with cells and tissues and triggers biological processes. Because of this, there is great interest in its use in medicine. The cold plasma literature describes a wide range of medical applications. Some are already in clinical use or in clinical trial phases, some are theorized based on animal studies or in vitro experiments. The multitude of proposed uses surely can make it seem like cold plasma is being promoted as a panacea. Panaceas have always been (rightfully) treated with great suspicion in medicine, but this does not mean that there cannot be medications and treatments which are effective for a wide range of different maladies. Dermatologists know at least one great example: corticosteroids, which we use to treat autoimmune diseases, genetically determined conditions, inflammatory diseases, certain malignancies, and even infections. It is possible because corticosteroids can influence pathways that are the common denominators of these very different conditions. Of course, the key is that we do not use them all the same way, all the time. No dermatologist would treat seborrheic dermatitis with systemic steroid or intralesional injections, but we achieve good control when using it in a cream. We do not treat acne with steroid creams, but we do use intralesional steroid injections. We quickly give patients corticosteroid pills for an allergic contact dermatitis caused by poison ivy, or even flares of eczema, but we do not treat psoriasis with systemic steroids. Yet, the first line of treatment for psoriasis is topical steroids, just as we use topical steroids for eczema but also for
the early stages of cutaneous T-cell lymphoma, a cancer. It is all in the details: different delivery routes, different corticosteroid molecules with different potency, and different concentrations and vehicles are used, based on the particular scenario.

Perhaps, being used to prescribing at least one panacea many times every day in my practice is what makes me open to the seemingly boundless benefits of cold plasma. I believe that in cold plasma we have a tool that can be used to effect key changes in biological targets, changes that can be common denominators to treat various, seemingly different diseases. Cold plasma can be generated with different devices and can be delivered in different ways. The composition of plasma can be adjusted, and the delivered amount can be controlled. The characteristics of cold plasma treatment can be adapted to organs, lesions, and conditions we treat with it, very much like corticosteroid treatment. The following will be a summary of the current utilization of cold plasma in dermatology, with a discussion of possible future areas and ways of expansion.

II. CLINICAL AREAS OF COLD PLASMA USE IN DERMATOLOGY

A. Wound Healing and Skin Regeneration

One of the very well established effects of cold plasma is inhibition of bacteria\(^1\),\(^2\) which has led to its use in ulcers.

Chronic ulcers, typically on the lower legs, can be traced to factors such as issues with circulation, microcirculation, and bacterial colonization that usually act in combination. Ulcers can be especially challenging to treat, while they cause significant morbidity as a chronic health problem. Because the presence of bacteria is an important element in ulcer pathogenesis, it is logical to assume that reducing the bacterial load promotes healing.\(^3\) Clinical trials used argon jet plasmas to good effect.\(^4\) Floating-electrode dielectric barrier discharge (DBD) plasma has also been tried with measurable reduction in bacterial load and ulcer size.\(^5\)

A recent trial compared cold plasma to traditional wound care in the treatment of chronic wounds and found plasma superior as assessed by the Pressure Ulcer Scale for Healing.\(^6\) It seems, however, that it was not only about reducing bacterial load: one trial found cold plasma beneficial for healing skin graft donor sites in a split-site comparative setup where bacterial colonization was removed as a factor.\(^7\) The wound healing results may be related to plasma’s effect on stem cell differentiation, which has been demonstrated in nonhuman experiments.

Cell culture\(^8\) and organ culture studies have shown that cold plasma treatment promotes differentiation of chondrocytes and osteoblasts and mouse limb bud growth and survival, likely by influencing Wnt signaling via reactive oxygen species.\(^9\) One study demonstrated that cold plasma treatment promotes epidermal cell proliferation, and increases skin remodeling when compared to untreated controls, both in HaCaT human keratinocyte culture and in an in vivo mouse model.\(^10\) It also showed that the effect was mediated by β-catenin activation and translocation to the nucleus in both models. As β-catenin activation is profoundly linked to Wnt signaling, these findings agree with the results of mouse
limb bud growth experiments. Other studies, which looked at plasma induced gene expression and cytokine production profile changes in cell cultures and mouse models, found an upregulation of collagen type I and alpha-SMA (which play a role in wound healing), increased proangiogenesis factors, and increased expression of genes like Type I collagen, fibronectin, and VEGF (which play an important role in maintaining skin function).

It appears that, instead of having one single target, cold plasma exerts a complex influence on a variety of factors which ultimately improve wound healing and skin function. Beyond healing wounded skin, a profound effect on intact skin was seen in rats, where jet plasma treatment of the skin increased fibroblast proliferation, collagen fiber synthesis, and epidermal thickness. Reduced collagen production and fibroblast activity are important elements of chronological skin aging, and if cold plasma can reverse that process, it means that it can play an important role not just in wound healing but in skin remodeling and rejuvenation as well. The substantial differences between, for example, leg ulcers, surgical wounds, or whole face applications, are device engineering challenges and the need to adjust and fine-tune plasma delivery parameters to meet practical needs, such as acceptable length and frequency of treatments, efficient delivery of cold plasma to large, incongruent surfaces.

B. Antineoplastic Effect

In a sense, the opposite of the pro-wound-healing and pro-skin-remodeling effect is that cold plasma can selectively induce cell death in malignant cell lines. There is extensive in vitro research exploring mechanisms and pathways. Although this selective “anticancer” effect seems to be universal and can be observed in cells of different tissue origin, in order to build a foundation for clinical use, it is still important that it also be demonstrated specifically in skin cancer cell lines. Cells of melanoma, the most impactful of skin cancers, were studied early on, and it was shown that both DBD plasma and helium jet plasma induced their apoptosis.

The selective apoptosis-inducing effect of cold plasma has also been shown in squamous cell carcinoma cell lines. However, these effects are not binary: dosing and delivery environment influenced them, and there were variations between different cancer cell lines from different tissues, meaning that treatment settings need to be optimized to the specific cancer target. Detailed examination of dose-based effects using surface microdischarge plasma on cultured melanoma cells showed that changing exposure time results in a switch from proapoptotic to procaspase senescence. It is clear that translating in vitro delivery settings to clinical use is a nuanced and complex process, further complicated by the anatomy of cancers such as size and location. It is likely that extensive optimization trials will have to take place before cold plasma can be used as a routine treatment for skin cancers.

Clinical trials involving cancers are contentious, both from an ethical and a regulatory perspective: the risk posed by undertreated or untreated malignancies must be addressed and an acceptable solution developed. Animal models for skin cancers are not always reliable. Fortunately, dermatology has a skin condition that can be used as
a “surrogate” target to test the feasibility of using cold plasma to treat at least one type of skin cancer: squamous cell carcinoma. This skin condition is actinic keratosis (or solar keratosis). It is viewed as a precancerous lesion, on one end of the spectrum of keratinocyte cancers. These red scaly skin growths are commonly found in sun-exposed areas, mostly in older individuals with lighter skin color. There are multiple treatment modalities, but none is perfect.22

Developing an effective and well-tolerated treatment for actinic keratosis is itself an important goal. Given its relationship with squamous cell carcinomas of the skin, its successful treatment with cold plasma can be helpful in multiple ways. It would justify trials of cold plasma for low-risk cases of squamous cell carcinoma. Actinic keratosis treatment can also be used to optimize dosing and delivery of cold plasma treatment with the expectation that these parameters can be transferrable to squamous cell carcinoma treatment at least as a starting point.

Two approaches have been reported for cold plasma treatment of actinic keratosis. Our group pioneered the use of a DBD plasma device to perform a so-called lesion-directed treatment, where individual lesions diagnosed as actinic keratosis were treated. In this proof-of-concept study of five patients, we treated 17 actinic keratosis lesions only one time. One month later, nine lesions had resolved fully and three had improved significantly, equaling a 53% clearance rate and a 70% rate of at least significant improvement or clearance. The treatment was completely painless and there were no reports of after-treatment inflammation, scab or blister formation, or any discomfort.23 We used a pulse generator creating nanosecond pulsed electric current and an elongated quartz-covered copper electrode.

Later, another group used a very different strategy: field-directed treatment, where an entire area with multiple actinic keratoses were treated and the lesion count, instead of individual lesions, was used as the measure of success. This approach has gained ground in dermatology, as it treats very early visually undetectable actinic keratosis lesions as well. This study involved seven patients. Target areas were treated twice a week, seven times total. The authors presented before and after total lesion counts and counts of improved lesions according to an actinic keratosis severity scale. They found that total lesions decreased by 23% and that 53% of lesions were given a lower grade, marking clinical improvement. Patients tolerated the treatments well.24

In a step forward, a follow-up randomized, prospective rater-blinded study compared cold plasma and a prescription topical medication (diclofenac gel, a well-established and commonly used actinic keratosis treatment) for the field-directed treatment of actinic keratosis. The authors showed that not only was cold plasma significantly more effective than diclofenac but it also produced fewer side effects.25 One of the limitations of this approach is that the treatment protocol calls for twice-weekly treatments over three months, which can become a practical difficulty for patients as they need to schedule office visits for the treatments. Another, potential limitation is the cost of treatment, which includes the initial investment in the device itself. Such limitations, however, can likely be at least partly addressed by optimizing delivery and device design and manufacturing.
While further trials with longer follow-up periods are needed, these studies have certainly shown that cold plasma is a legitimate treatment for actinic keratosis, and have helped pave the way to introducing clinical trials examining cold plasma treatment of skin cancer.

C. Treatment of Warts

*In vitro* experiments indicate that cold plasma can destabilize adenoviruses,\textsuperscript{26,27} which are nonenveloped double-stranded DNA viruses just like human papilloma viruses, the causative agents of cutaneous warts. That in itself is sufficient justification to consider using cold plasma to treat warts, but recent advances in our understanding of wart treatments open the door for another pathway to be considered. There is new evidence that imiquimod cream (a well-established antiwart topical medication thought to induce toll-like receptor–dependent immune response) may act at least in part by inducing intracellular calcium influx, which leads to endoplasmic reticulum stress and apoptosis, in a toll-like receptor–independent manner.\textsuperscript{28} Heat therapy, which has been shown to be effective against warts,\textsuperscript{29} also may work by triggering calcium influx, as shown by studies examining the effect of hyperthermia on epithelial tumor cell lines.\textsuperscript{30} It has long been established that plasma induces intracellular calcium influx, meaning that it may have an apoptosis-inducing effect on warts as well.\textsuperscript{31}

The first proof-of-concept clinical study of cold plasma treatment of warts, by our group, demonstrated its efficacy in adult patients using the same DBD plasma device we used for actinic keratosis treatment.\textsuperscript{32} An important factor distinguishing it from any currently used wart treatments is that cold plasma is entirely painless and there is no discomfort, blistering, or inflammation after the procedure. In a follow-up study, we demonstrated the efficacy and exceptional tolerability of cold plasma to treat warts in children. Five patients with a total of 28 warts on their hands and feet were treated. Treatment sessions were scheduled four weeks apart. All lesions were cleared after an average of only two treatments.\textsuperscript{33} There was no recurrence during the follow-up period, which lasted 6–10 months post-treatment.

Many modalities are used for the treatment of warts today, but they all have significant drawbacks that include suboptimal efficacy, pain, after-treatment inflammation, discomfort, discoloration, and scarring.\textsuperscript{34} Warts frequently affect children, a patient population where painless cold plasma treatment is even more significant. Cold plasma can also be used in cosmetically sensitive areas as it does not induce inflammation, scarring, or discoloration. If large-scale studies confirm the outstanding efficacy of cold plasma as shown in our small studies, it can certainly become a very desirable treatment modality for warts.

D. Acne Treatment

One of the “bread and butter” diseases of dermatology is acne, an inflammatory disease of the sebaceous follicles whose development results from many factors. Just as in the case of leg ulcers, the role bacteria play in the pathogenesis of acne makes this condition a feasible target for cold plasma. A semispheric DBD electrode to treat acne has been
reported to reduce both the number of acne lesions and propionibacterium colonization of the skin. A recent case report of two patients treated with an argon-jet plasma torch device once a week for several weeks found cold plasma to be an effective and well-tolerated treatment for acne based on clinical assessment and related metrics such as sebum production.

Both reports are limited by very small numbers of cases, but they are encouraging given that acne is another area in dermatology which lacks definitive solutions. One of the obstacles for cold plasma in treating acne is that the treatment must be evenly applied to a large, incongruous surface (the face) in a time-efficient manner. DBD electrodes and single-jet plasmas reach a relatively smaller surface, but both can be moved around continuously to cover larger areas. This, however, introduces a variable. It is difficult to standardize speed and even coverage of all areas, especially concave surfaces, and this can lead to varying operator-dependent outcomes. A way to avoid this is the use of devices that treat a larger surface without being moved and timing exposure.

One approach is a plasma torch, such as used in the above-referenced case report. Another is a variation of the DBD electrode concept, surface microdischarge plasma, which can generate a substantial amount of plasma on a larger target surface without an external gas supply. Many “classical” acne treatments are antibiotics: topical or systemic. In line with our overall goal in medicine to reduce the use of antibiotics, dermatology is always in search of nonantibiotic acne treatments. It remains to be seen if cold plasma devices can achieve this in current acne treatments.

E. Onychomycosis

Another condition lacking highly effective treatments is the fungal infection of nails. Laboratory experiments indicate that, at least in theory, cold plasma may offer a solution. In an ex vivo study, it was found that argon-jet plasma inhibits the proliferation of Trichophyton interdigitale, Trichophyton rubrum, Microsporum canis, and Candida albicans. In an in vitro experiment, Trichophyton rubrum and Microsporum canis growth was stopped by daily 10-minute surface microdischarge plasma treatments for nine days. In another ex vivo model, helium jet plasma inhibited Trichophyton rubrum adhesion, germination, and growth.

A clinical pilot study used DBD plasma on the toenails of 19 patients. Treatment was performed three times a week for several months and resulted in 50% clinical and ~15% mycological cure (13 patients completed the study). Frequent office-based treatments over several months may not be practical for many patients. If the delivery strategy is improved, cold plasma will certainly be a welcome addition to the rather short list of treatments available for this condition.

F. Diseases Caused by Arthropods

So far, only a single arthropod-caused dermatological condition has been targeted for plasma treatment: head lice. One trial used an ingenious device, a plasma comb, which
generated cold plasma between comb-tooth–like electrodes, effectively killing the lice. The authors performed an elaborate safety analysis as well. An easy-to-use and effective cold plasma treatment may become very important as resistant “super” lice are reported more frequently.

G. Hair Loss Treatment: Effects on Stem Cells

As described in the context of wound healing, cold plasma has been shown to influence stem cells by promoting growth and differentiation in various tissues, partly via the β-catenin and Wnt pathways, which are well known to play an important role in keratinocyte differentiation. Another, also previously mentioned, effect of plasma is the induction of cellular calcium influx. This may be a connection between cold plasma and stem cells—hair follicle stem cells specifically—as it has been shown that calcium channels are important in determining their behavior. Furthermore, the widely used androgenetic alopecia treatment minoxidil seems to induce stem cell differentiation and hair growth via triggering cellular calcium influx.

As cold plasma can induce cellular calcium influx, and cellular calcium influx is the likely way an established hair loss treatment works, it is reasonable to expect that cold plasma can also treat hair loss. While it was not an animal model for hair loss, a recent study found that rat hair follicle diameter increased (along with fibroblast proliferation, collagen fiber synthesis, and epidermal thickness) after treatments with cold plasma jet. The human scalp is thick, making it potentially challenging to apply cold plasma in a way that reaches the hair follicle stem cells, not to mention the difficulties of performing this on the entire scalp surface and with hair in the way. A possible solution is the use of a plasma-treated vehicle, a concept explored in many in vitro experiments. In short, liquids exposed to plasma may exert some of the same biological effects as plasma itself, which we will review in the context of delivery systems. Our group conducted a clinical trial using plasma-treated liquid to treat androgenetic alopecia (male or female pattern hair loss) based on the above principles. Preliminary assessment showed that ongoing indirect plasma treatment for the scalp is well tolerated and preferred by patients, and clinical assessment revealed some hair growth. This study was a small pilot, primarily designed to assess the tolerability and practicality of this treatment modality. Any positive effects on hair growth should be looked at very cautiously and in that context only. Appropriately designed, larger trials will be needed to confirm the ability of cold plasma to induce hair growth.

III. PRACTICAL ASPECTS OF COLD PLASMA DELIVERY

A. Plasma Composition

Cold plasma is a complex entity and its composition, the concentration of free radicals and charged particles, changes according to the circumstances of its creation, along with additional factors that may impact treated tissues, such as UV radiation and electric...
field. The type of device used, gas (or air), and device settings make all the difference. On one hand, it means that cold plasma effects created with one device cannot simply be expected to be reproduceable by another. On the other hand, this gives us tools to create just the right amount and composition of plasma we need for a specific goal—very important for medical applications as even if we consider only applications for dermatology, the requirements change with differently treated diseases. The size of the area that needs to be treated, required penetration depth, and the ideal plasma composition can be very different. For example, it has been demonstrated that the ability of cold plasma to induce apoptosis in melanoma cells in vitro is exposure time–dependent. Changing the gas used for the very same jet device changes the cold plasma effect on bacterial growth. A 3D skin model–based study found that modifying exposure time, energy input, and carrier gas changes how cold plasma effects interleukin expression.

Given all the variables of cold plasma, and the unanswered questions regarding the way it actually exerts its effects on cells and tissues, optimizing treatment conditions will require extensive clinical trials and in vitro studies, such as biological assays to evaluate the effects of cold plasma devices.

B. Tissue Penetration of Cold Plasma

In terms of plasma “dosing,” depth of penetration is crucial. In vitro studies provide some insight. One experiment performed on pig muscle revealed a penetration depth difference between plasma components: Reactive oxygen species penetration of 0.5 mm of tissue was 5%, while reactive nitrogen species penetration was 80%. One study detected the penetration of cold plasma reactive species through 1-mm-thick pig skin and multiple millimeters of agarose gel. Differences in the penetration depth of various species and while using different plasma settings were reported. The same study reported that cold plasma induced apoptosis throughout a 2.8-mm-thick tumor in a mouse.

Tissue penetration is likely to be based on more than just thickness; other plasma–tissue interactions may play a role as well. Biological liquids on a treated surface change the depth of penetration and the makeup of cold plasma–derived reactive species that reach the target depth of the treated tissue. In general, however, at least as far as depth is concerned, it seems that cold plasma should be able to penetrate the entire epidermis or at least the superficial dermis. The subcutis may be beyond its reach, at least in areas where the dermis is thicker.

C. Direct Plasma Delivery Systems

Currently, the cold plasma delivery methods most common in clinical settings are plasma jet, DBD plasma, and surface microdischarge plasma. Detailed descriptions of these devices fall outside the scope of this review. Comparative clinical experience with different devices is very limited. One application that allows some degree of indirect comparison is actinic keratosis treatment.
Previously, we described how two very different types of devices have been used successfully for this condition. The first was a DBD plasma. A small electrode tip was used to target few-millimeter-sized lesions individually. This approach resulted in good clinical outcome following only one treatment, likely because of the concentrated delivery of potent plasma. A jet plasma was used subsequently as a field treatment for the same condition. It allowed treating a larger area, making it possible to treat multiple lesions at the same time and also reduce field cancerization. The flip side was that, unlike the single treatment of DBD plasma, it required multiple twice-weekly treatment sessions. For some applications, like some cases of actinic keratosis or warts currently and malignancies in the future, the concentrated, single lesion approach is ideal. A device able to treat a larger surface would work best for other conditions, such as acne, where the condition is ongoing and numerous lesions are present in various stages of development at all times, some possibly as yet clinically undetectable (much like actinic keratosis and field cancerization).

While plasma torches inherently cover a large area, regardless of surface unevenness, DBD plasma electrodes can also be engineered so they cover a bigger field. Another option is to move the electrode over the treated area. The clinical feasibility of this has already been explored in acne treatment. Surface microdischarge plasma has proven to be a reliable way of treating ulcers and will likely be useful for other, larger surface treatments. Beyond optimization of the delivered cold plasma, device design and engineering must meet the challenge of creating a tool that is practical for daily clinical practice. Intuitive control interfaces, reproducible and standardized treatment flows, and easy-to-manipulate equipment are all very important from the standpoint of a clinician. These can be critical in determining the success of cold plasma as a clinical tool. Addressing device safety is also a must, and there is an ongoing process to develop international standards, as discussed elsewhere.

D. Indirect Plasma Treatment

An entirely different plasma delivery system with great promise for dermatology is indirect plasma: exposure of a liquid to cold plasma, which liquid can subsequently be used to deliver plasma effects. This method is used extensively for cell culture–based cold plasma experiments. As if cold plasma generation were not complex enough itself, indirect plasma introduces even more variables. Plasma-liquid interactions, plasma source, and liquid type, alter the composition of reactive species in the liquid. Besides simply “mixing” with liquid and having a physical interaction, cold plasma induces chemical and biochemical reactions as well, which also change the final product. Just as with direct plasma treatment, all of these possible variables allow us to fine-tune our plasma-treated liquid according to our therapeutic needs.

Clinical experience with indirect plasma in dermatology is limited. As referenced above, our group conducted a pilot study that involved twice-daily application of cold plasma–treated liquid to scalp skin for six months. The application was well tolerated and produced no adverse effects. We used an alcohol-water mixture as the treated liquid,
but other liquids, or, feasibly, gels and creams, can be used based on the specific needs of the treated area and the condition. The potential for indirect plasma treatment in dermatology is immense, as it may help to overcome some of the limitations of direct cold plasma delivery. Indirect plasma can be applied to any area of the skin without size and surface limitations. It can also be potentially used as an injected, intralesional treatment. For repeated, ongoing treatment regimens, indirect plasma eliminates the need for a device to be present at the treatment site.

Depending on how long the biological effects last, after creating it indirect plasma can be stored, increasing distribution options. As we have seen, cold plasma may not be able to penetrate deep enough to reach structures on the subcutis, such as hair follicles and sweat glands. However, topically applied medications are known to reach these levels. Suitable topical medication vehicles treated with cold plasma may be the solution to the problem of penetration depth limits.

Lastly, from a safety standpoint, indirect cold plasma eliminates from the treatment area UV radiation, ozone, strong electrical fields, and electricity, thus reducing safety concerns. Like nearly all other subfields of plasma medicine, indirect plasma is also in need of a substantial amount of in vitro and clinical research before it can be reliably used to treat patients.

IV. POSSIBLE FUTURE APPLICATIONS IN DERMATOLOGY

The following are some areas where it is reasonable to expect that cold plasma will have something to offer to dermatology. However, this hypothesizing is based only on indirect data, not clinical trials.

A. Biofilm and Microbiome

Cold plasma use in dermatology started with its deleterious effect on bacteria. A type of eczema called atopic dermatitis, a common chronic inflammatory skin condition, has a close connection to *Staphylococcus* containing biofilm, which has been suggested to play a crucial role in itching, an important symptom of the disease.\(^6\)\(^0\) Cold plasma is known to disrupt biofilms\(^6\)\(^1\) and thus may offer a possible treatment for this condition. A clinical study showed no benefit from cold plasma treatment compared to placebo when used to treat itching associated with different skin conditions.\(^6\)\(^2\) However, if used in the specific group of atopic dermatitis patients, the outcome may be different. Atopic dermatitis may affect very large areas, often nearly the entire skin surface. While treatment of the whole human body using our current direct cold plasma treatment devices is not possible in a practical way, indirect plasma treatment may offer an alternative.

Gut microbiome is now a well-established entity. Its disturbances are implicated in a number of medical conditions. In recent years, skin microbiome emerged as a similarly important collection of microorganisms. It has been tied to skin diseases such as acne (a logical connection given the role *Propionibacterium* plays in acne),\(^6\)\(^3\) psoriasis (a genetically determined inflammatory skin disease),\(^6\)\(^4\) inflammatory hair follicle
disorders causing scarring alopecia, and even unlikely diseases like acral melanoma. Cold plasma treatment can certainly be used in a simple manner to reduce the number of bacterial and fungal organisms on the skin, and that may be sufficient in some cases. But we saw how changes in plasma characteristics influence its effects on cells and tissues. It has been demonstrated that plasma does not affect different fungal organisms the same way. If fine-tuning cold plasma allows the selective inhibition of specific types of bacteria and fungi, it may open the way to use it alone or in combination with other interventions, not just to suppress the microbiome but to normalize it.

B. Arthropod-Caused Skin Disorders

A previously mentioned study reporting the successful treatment of head lice using a plasma comb can be seen as a proof-of-concept for other arthropod-related dermatoses. While those are few in number, they are often treatment resistant. Scabies, a highly contagious parasite infection, is one of them, where treatment resistance is a growing issue. Indirect cold plasma treatment could offer a new antiparasite option. Another complex skin disease, in which arthropods play at least some role, is rosacea. Overgrowth of Demodex folliculorum mites, which are normal colonizers of the human skin, has been proposed as a possible mechanism, leading to the introduction of a topical antimite treatment for rosacea.

It has not been shown that cold plasma can kill Demodex mites, but the results of the lice treatment study raise this possibility. Rosacea can be clinically similar to, and often overlaps with, acne. Many treatments are used for both disorders. Given the demonstrated benefits of cold plasma in acne, combined with its possible ability to reduce Demodex mite counts, it is reasonable to hope that it may become a useful treatment for rosacea.

C. Cutaneous Malignancies

We have seen how in vitro studies, animal experiments, and now the successful treatment of actinic keratosis using different approaches and plasma sources opened the door for treatment of skin cancers. For small, single skin cancers, the approach can be straightforward. One unique skin cancer is cutaneous T-cell lymphoma, which usually progresses very slowly but can involve large areas of the skin. Herein lies the treatment challenge: effectively delivering a treatment that can stop cancer cell growth yet is not harmful even when used on a substantial portion of the skin surface. Dermatologists use full-body ultraviolet light and topical medications, for example, but these have side effects: ultraviolet light therapy carries a risk of skin cancers; topical steroids may cause skin atrophy after long-term application and may suppress adrenal function via systemic absorption.

If indirect plasma treatment is found to be effective, it will become a useful addition to our toolbox. For solid cancers, another consideration is intralesional injection of plasma-treated liquids. Skin cancer surgeries rely either on predetermined normal skin
margins or on microscopic control of margins to avoid leaving behind small, clinically undetectable groups of cancer cells. Extensive *in vitro* research shows that indirect cold plasma treatment selectively induces cell death in cancer cells via a plasma-treated medium. If this effect can be fine-tuned to effectively treat skin cancers *in vivo*, not only the clinically detectable skin cancer mass but the surrounding skin can also be infiltrated using intralesional injections. This could have the effect of completely destroying a skin cancer in a way that is equal to having surgical margins but without the tissue damage and scarring associated with actual surgery. Of course, substantial research will have to be conducted to develop cold plasma into a successful treatment for skin cancers.

### D. Skin Rejuvenation

We have discussed, in the context of both ulcer treatment and hair loss treatment, cold plasma’s well-documented promotion of stem cell differentiation and tissue regeneration. Available skin-specific organ-level data are limited, but one example is the previously cited animal study showing that cold plasma treatment induces increased epidermal thickness and collagen formation.\(^\text{15}\) One clinical observation comes from a study of cold plasma treatment of actinic keratosis in which the authors observed signs of a skin-remodeling effect after treatment.\(^\text{24}\) We have sufficient experimental data to justify exploring cold plasma as a tool to reverse processes associated with aging by its effect on cutaneous stem cells. This is of course important for cosmetic dermatology; it is also important because aging skin is more susceptible to certain skin disorders and because the same concepts can be used to treat degenerative skin diseases.

### V. CONCLUSION

As we have seen, cold plasma has been clinically shown to have great potential as a treatment for a variety of skin conditions. As devices continue to evolve and with the introduction of indirect plasma, even more skin diseases can be targeted. Perhaps the biggest promise lies in the adjustability of cold plasma treatment. It gives researchers a way to develop just the right treatment for the condition they are attempting to treat. Cold plasma’s ability to influence the skin microbiome, to selectively kill cancer cells, and to induce tissue or skin appendage regeneration gives us tools that can have a major impact on how we treat skin disorders.

Dermatology often benefits from other areas of medicine: treatments and concepts have been transformed to fit its needs. Skin is outside and thus easily accessible to plasma treatment, which relies on delivering either plasma or plasma-treated liquids directly to the target site. This puts skin at an advantage compared to internal organs, where delivery is more difficult. It seems that when it comes to cold plasma medicine, dermatology may be the pioneer: solutions developed for skin diseases will possibly serve as templates to treat other organ systems as well.
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