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Chronic inflammation induced by microneedling and the use of bone marrow stem cell cytokines

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ABSTRACT

Physicians advocating the frequent use of microneedling for skin care are advocating for a potentially dangerous procedure, especially when coupled with the topical application of bone marrow stem cell derived cytokines. Not only are the physicians who advocate for frequent microneedling as a skin care procedure not Board Certified in Dermatology (FAAD or FAOCD), they are not dermatologist; rather they are family practitioners. Further, they don't have M.D. or D.O. medical doctorate degrees, rather they have truncated bachelor in medicine degrees with limited education and training. Unlike board certified dermatologists, these physicians simply have neither a deep knowledge of dermatology, nor knowledge of the immunology of the skin. These physicians have developed and promulgated books, blogs, and training classes for these procedures that are offered to non-physicians, often to estheticians. Advocating the frequent use of microneedling for skin care, especially when coupled with the topical application of bone marrow stem cell derived cytokines induces a damaging chronic inflammatory state in the skin, and likely systemic inflammation too. Microneedling of the skin, even under sterile conditions, elicits a sterile inflammatory response, including early recruitment of neutrophils, throughout the layers of the skin, and even systemically. Given the non-sterile nature of the skin, a rich microbiome, including bacteria, viruses, and fungi, at the skin's surface, these procedures may allow microneedling to cause these microorganisms to gain entry into the epidermis and dermis, furthering an inflammatory response already induced by the wound and associated inflammatogenic self-molecules. The use of bone marrow stem cell cytokines can amplify the inflammatory response induced by injury, instead of resolving the inflammation such as that by the pro-resolving effects induced by adipose derived mesenchymal stem cells and fibroblasts acquired from skin tissue.

Sterile inflammation, including an early innate immune response involving neutrophils [1], has evolved as a physiological response to tissue injury and is an aspect of wound repair and the restoration of homeostasis. However, like any potent immune response, when overactive such as in repetitive or constant injury, or environmental and lifestyle factors, such as topical products that induce inflammation or repeated microneedling procedures, the sterile inflammatory response becomes pathological. The human epidermis ranges in depth between about 30 and 100 μm depending on a number of parameters, including the area of the body measured, with facial areas being amongst the thinnest [2–4]. The shortest microneedles used for procedures are 0.25 mm (250 μm) and the longest are 2.5 mm (2500 μm), and actual penetration depths as measured by an F.C.A.S. accredited plastic surgeon range from 235 μm for the 0.25 mm needles up to about 2000 μm for the longer needles [5]. The channels created by the microwounding allowed optimal penetration of topically applied molecules at about 5 min post-procedure with significant penetration lasting for 30 min. Thus, even the shortest needles used for microneedling (0.25 mm) will induce wounding of the epidermis (100 μm) and dermis, with the physical wound lasting for at least 30 min, and the induction of inflammation lasting significantly longer (see Fig. 1).

Transient mechanical forces in wounding will cause the skin's scaffold of normal, adult cell-cell and cell-ECM contacts to be interrupted and the colony of cells in the wounded area to change their phenotypes for a period of days [6]. Antonio et al. [7] observed tumor formation at sites of the animal that are particularly prone to friction or damage. Wounding that induces skin tumors has been found in mice that express a mutated oncogene or had been pretreated with a mutagenic chemical develop papilloma at the site of a skin injury. Likewise, wound-related melanoma formation in oncogene-sensitized mice has been previously reported [8]. [9] tested whether injury and tumor development may be causally connected, and found evidence for this in their zebrafish model.

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The age-old hypothesis that tumors are wounds that never heal, was given credence when Fuch's lab [10] unearthed a striking lineage infidelity phenotype in stem cells that arises transiently in a wound response and persists in malignancy. The lineage infidelity of the cells, if persisting in a state of stress, leads to an increased probability of cancer.

Skin wounding, including that caused by microneedling, induces, if done in sterile conditions, sterile inflammation or self-debris. Self-debris released as a consequence of cell and organelle injury, without infection [11], and their products functions as endogenous "damage"-associated molecular patterns (DAMPs) that activate innate and adaptive immunity, including neutrophils and macrophages, and T cells. In the presence of damage-associated molecular patterns, NF-κB activation leads to hematopoietic stem cell (HSC) death, and contributes to the reduced HSC self-renewal potential of aged HSCs, and possibly systemic inflammation [12]. Such damage signals occurring in the epidermis are sensed by keratinocytes (KCs) and cause secretion of IFNβ by activated KCs, leading to further activation of the adaptive immune system and maturation of dendritic cells and T cell stimulation [13]. In age related dysfunction of the epidermis in a mouse model or disruption by tape stripping, proinflammatory cytokines are measured in the skin, as well as systemic proinflammatory cytokines measured in the blood [14]; the same results were found in humans [15]. Once keratinocyte stress is detected, the dendritic epidermal T cells (DETC) localized in the epidermis respond by the local secretion of chemokines, cytotoxic effector molecules, growth factors and cytokines that orchestrate skin inflammation, tumor killing, and a wound healing response [16]. A defining feature of sterile inflammation is that it can often result in chronic inflammatory diseases [17], and cancer [18]. Published in JAMA Dermatology [19] was the report of a lack of safety studies for microneedling, but, indeed, the continuing report of adverse events likely caused by microneedling? Not only did Soltani-Arabshahi et al. report facial allergic granulomatous reactions following microneedling, they also reported systemic effects including arthralgias in the joints and erythema nodosum in the fat layers proximal to the skin. Reports of these granulomatous AEs continue [20]. Some of the adverse events were shown to endure for at least 9 months. Systemic effects due to injury of the skin are not surprising given that [15] have shown that barrier function disruption, without disruption of the proximal epidermis and dermis of the skin will lead to not only proinflammatory factors in the skin, but these proinflammatory factors, such as IL-1b and IL-6 and TNFa, will increase systemically as they are found in the blood circulation of patients with barrier function disruption. The systemic inflammation in the circulation can be reduced by reparation of the skin's epidermal barrier function. Animal models have also shown that over expression of immune-related molecules exclusively in the skin results in systemic autoimmunity [21], even when that over expression is confined to the epidermis [22]. Disruption of barrier function not only induces cutaneous inflammation by stimulating proinflammatory cytokine release, but also induces inflammatory cell maturation and infiltration. Barrier disruption also increases the density of mast cells, a major source of histamine in the dermis, and a major cause of pruritus. The increased release of histamine by mast cells may also further disrupt epidermal barrier function by inhibition of keratinocyte differentiation [23] and inhibition of the production of proteins involved in barrier integrity [24]. Even when only the stratum corneum is disrupted, an innate immune response is fully initiated and developed, and an adaptive immune response is elicited, but may be somewhat dampened by IL-33 and consequent induction of Treg function [25]. Inflammatory cells and their chemical messengers are essential components of the tumor microenvironment [26]. Microneedling, through pressure effects alone, wounding, or exposure to air, can induce the release of ATP from keratinocytes [27,28]. In turn, extracellular ATP can induce a number of effects, including a proinflammatory response and proliferation [29].

Skin wounding can cause Basal Cell Carcinomas (BCC), and the carcinoma can arise from multiple stem cell populations, including the bulge and the interfollicular epidermis (IFE). BCCs derive almost exclusively from the epidermis, with a small minority of tumors arising from hair follicle infundibulum [30]. The originating cell can influence the subtype of BCC that develops and can also affect the likelihood that a tumor will form. During chronic wounding, the notable repair and homeostatic functions of macrophages are lost, which results in their involvement in the development of diseases, including cancer [31].

Damage in keratinocytes (KC) has been shown to cause a significant degradation of hyaluronic acid (HA) at the KC pericellular matrix, i.e. the HA immediately surrounding the KC. The decrease in HA deposition was correlated to an upregulation of HYAL 1 and 2, enzymes responsible for HA cleavage and the generation of low molecular weight-HA fragments found to induce inflammation [32]. The ensuing inflammatory response due to KC damage was initially mediated by reactive oxygen species (ROS), with the eventual induction of a number of cytokines including IL-18, a key mediator in allergic dermatitis [32]. Microneedling has been reported to cause an immune response when used for scar reduction [20], and the upregulation of IGF-1 in a three dimensional human skin model [33]. The Schmitt et al. study used a simplified skin model consisting of bovine matrix cultured with human fibroblasts. The immune system present in the normal epidermis and dermis was devoid in this model system. Therefore, a normal immune response to microneedling could not be analyzed in the [33] study. Microneeedling, given its wounding of the epithelium, will induce a release of EGF and activate EGF receptors [34]. In human melanoma-initiating cells, IGF-1

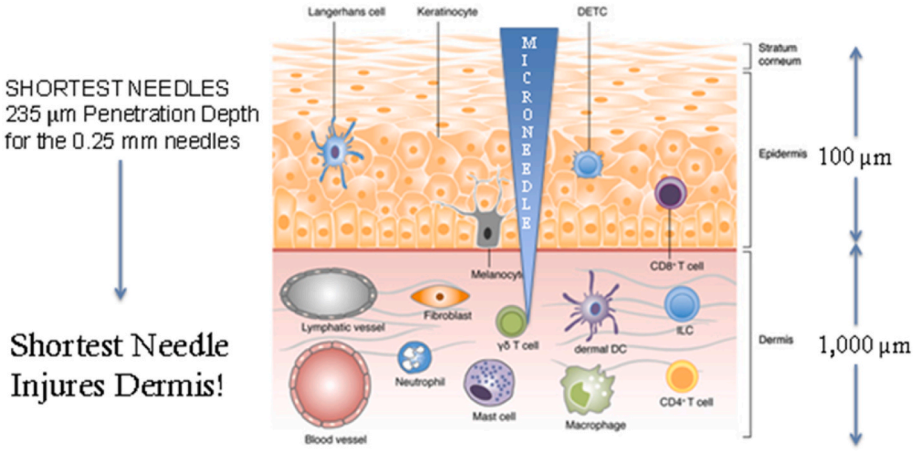

Fig. 1. A rich innate and adaptive immune system is located in the epidermis and the dermis. The shortest microneedles (0.25 mm) used for skin procedures penetrate through both the epidermis and the dermis.

has been shown to drive their expansion through an epithelial-mesenchymal transition (EMT) process [35]. In keratinocytes, IGF-1 stimulates membrane protrusion and facilitates cell spreading [36], and in mouse keratinocytes, crucial biochemistry for oncogenic HRAS oncogene initiation, the driver of squamous carcinoma, appears to involve the up-regulation of ligands for and autocrine activation of EGFR [37]. In cultured keratinocytes, EGF and IGF-1 work synergistically to promote keratinocyte proliferation [38]. Thus, microneedling can induce the release of both IGF-1 and EGF, two synergistic factors involved in the induction of cancer.

Also, after epidermal injury, stem cells from the bulge are recruited into the epidermis and migrate in a linear manner toward the center of the wound [39]. These migrating stem cells from the bulge express SmoM2 thus inducing these cells to form tumors [40]. Further, wounding of aged skin in the dermal layer, as can happen with even the shortest needles used in microneedling, will induce fibroblasts to release matrix proteins. However, the aged fibroblasts will fail to release all of the important matrix proteins, including HAPLN1, a protein that binds HA and glycoproteins, and important for preventing melanoma metastasis [41]. This is another mechanism through which cancer and cancer metastasis may be induced when aged skin is wounded, included during microneedling. One means to obviate the problem during wounding of aged skin may be to topically apply the secretome from young fibroblasts that contains HAPLN1 [41].

Further complicating the inflammatory response induced by microneedling, is the non-sterile nature of the skin, a rich microbiome, including bacteria, viruses, and fungi, at the skin's surface that microneedling may allow to gain entry into the epidermis and dermis, furthering an inflammatory response already induced by the wound and associated inflammatogenic self-molecules [42,43]. Indeed, microneedling of the skin is such an effective means to transmit microorganisms, including viruses that the procedure can be used to vaccinate against influenza [44].

Despite these data indicating an induction of innate and adaptive immune system inflammatory responses by microneedling, claims that "It is "repetitive" micro-injury of the epidermis, along with increased absorption of topicals sustained over prolonged periods, that achieves optimum results" have been made [45]. The authors claim that the shortest microneedles only injure the epidermis, but careful measurements find that the epidermis and dermis are injured by the shortest needles [5]. Repetitive microneedling as a skin care technique in combination with topically applied bone marrow stem cell (BMSC) cytokines has been advocated (https://www.prlog.org/12333438-stem-cell-skincare-products-benefiting-recovery-after-medical-aesthetic-treatments.html) and (http://barefacedtruth.com/2015/06/28/bfgf-microneedling-procollagen-anti-collagen/). These advocations are promulgated to a wide audience, mostly composed of non-physicians who are instructed to perform these dermatological procedures without qualification. Given that BMSC cytokines activate a number of inflammatory pathways [46,47], cause over proliferation [48] and consequential aging [49], cancer (Zu et al., 2012; [50], and fibrosis [51,52], the use of BMSC cytokines to further increase the inflammatory and cancer causing effects of repetitive microneedling are dangerous. An important danger in using BMSCs for donor stem cells is that they are often tainted with cancer cells [53], and this problem is often not recognized even under stringent screening of the donor cells. This problem is even underappreciated among physicians performing BMSC transplants [54]; Maguire, 2019B). For example, about one-third of patients diagnosed with localized breast cancer, carcinoma cells have already disseminated to distant anatomical sites, including bone marrow, at the time of initial cancer diagnosis (Pantel et al., 2008). The vast majority of these cells reside for extended periods of time in an apparently innocuous quiescent state. Once a tumor cell disseminates into the BM, the cancer cell often displays phenotypic characteristics of BMSCs rendering cancer cells difficult to distinguish from BMSCs [55]. Cancer cells can fuse with BMSCs and change their phenotype (Terada et al., 2020) or release exosomes to change the phenotype of BMSCs to cancer promoting [56]. Indeed breast tumor cells fuse spontaneously with bone marrow mesenchymal stem cells [57]. The molecules and exosomes that cancer cells release, potentially present in BMSC cytokines, are known to induce cancer [58–62]. Under the same conditions where cancer cell derived exosomes initiated cancer, dermal fibroblasts did not [62], therefore the exosomes specifically from cancer cells and potentially bone marrow stem cells may induce cancer.

Wounds share many phenotypic characteristics with tumors, including the increased expression of genes with oncogenic potential, the recruitment of immune cells, increased epithelial cell migration and proliferation, and recruitment of bone marrow stem cells (BMSCs). For example, analysis of human prostatectomies showed that BMSCs represented 0.01–1.1% of total cells present in the prostate tumor [63], and BMSCs also home to wounded skin [64]. Biochemical pathways used by BMSCs for trafficking are the same as those used by tumor cells for metastasis [65]. For instance, chemokines and cytokines produced during chronic inflammation of wounded skin, such as SDF-1, influence the behavior and migration of cancer cells. These are the same chemokines and cytokines responsible for physiological stem cells homing back to the marrow cavity. The blood also brings SDF-1 to the skin, expressed by BMSCs and contained in their exosomes (Wang et al., 2014) that promotes the scarring of skin [66], another risk factor for cancer [67,68]. [69] found that a surgical wound with an acute inflammatory response could cause dormant breast cancer cells in mice to start growing and spreading. Thus, the postsurgical wound-healing, inflammatory response was found to be responsible for the early eruption of previously dormant cancer cells at distant anatomical sites. Like the early phase of a wound without infection, neutrophils are actively recruited to the wound [11], including the wound that a growing tumor makes. Once there, they may contribute to the cancer's progression. In some cancers, such as melanoma, the presence of neutrophils around the tumor correlates with a poorer prognosis [70].

BMSCs are normally only called into action, migrating to and releasing their cytokines into the skin, even into the epidermis [71], only during a major wounding event, often with associated infection. Once they are recruited into the skin, BMSCs can change phenotypes into a cancer associated fibroblast (CAF) and have been found to be a contributing factor to skin neoplasm development [72,73]. As such, BMSC cytokines activate a major inflammatory, proliferative state to fight infection and close the wound. As chronic wounds have been likened to cancer [74,75], chronic application of BMSC cytokines, just as seen during the release of BMSC cytokines during chronic wounds, may also be likened to cancer.

1. Safety considerations: ADSCs preferred over BMSCs

When addressing safety and efficacy concerns of the stem cell types used to derive their exosomes/secretome, we must consider tissue specific stem cells [76]. Choosing the appropriate stem cell type to match the condition to be treated is critical not only to efficacy, but most importantly, safety of the therapeutic. Beyond the genetic and epigenetic factors that influence stem cell phenotype as embryonic stem cells differentiate into somatic stem cells [77], the immediate niche of the stem cell will have profound influence on the cell's phenotype [76]. As previously described [78] the molecules released from adipose derived mesenchymal stem cells (ADSCs) and fibroblasts can be used renormalize the immune system in epithelial tissue in general, and even be used for application to the upper respiratory tract to better prevent and remediate Covid-19 and other viral diseases. The stem cell technology is likely to work well when combined with nasal vaccination [79]. This is in contradistinction to bone marrow mesenchymal stem cells (BMSCs), that exhibit some potentially dangerous characteristics that should limit their use in therapeutic development.

The complexity of the bone marrow (BM) niche can lead to many stem cell phenotypes, whether we consider hematopoietic stem cells

(HSCs) or bone marrow mesenchymal stem cells (BMSCs). Here I will discuss the properties of BMSCs, not HSCs. Because of the complexity, many BMSC phenotypes exist, including disease causing phenotypes that are varied and hard to distinguish [80] – a part of the problem in using BMSC for therapeutic development. This complication, unlike that for ADSCS, includes recirculated cells, particularly recirculated cancer cells. Once a tumor cell disseminates into the BM, the cancer cell often displays phenotypic characteristics of BMSCs rendering cancer cells difficult to distinguish from BMSCs [55]. BM is a site of BMSCs that may differentiate into HSCs [81] and recirculating blood cells that may differentiate into BMSCs [82,83]. BMSCs are also found outside of the niche in peripheral blood [84] and home into sites of injury [85] and cancer tissue where they are educated into becoming a pro-cancerous phenotype [86]. Recirculated melanoma and myelogenous leukemia cells [87] in BM interact with BMSCs to change the phenotype of the BMSC to one that is cancer promoting by enhancing their proliferation, migration, and invasion and altering the production of proteins involved in the regulation of the cell cycle [88]. Indeed, melanoma tumor cells start to disseminate to BM during the initial steps of tumor development [89]. In breast cancer patients, detection of recirculated cancer cells that disseminated in BM predicts recurrence of the cancer [90]. Cancer cells can fuse with BMSCs and change their phenotype [91], or release exosomes to change the phenotype of BMSCs to cancer promoting [56]. Indeed breast tumor cells fuse spontaneously with bone marrow mesenchymal stem cells [57]. This fusion may facilitate the exchange of cellular material from the cancer cell to the BMSC rendering the fused cell more oncogenic [92]. Further, others have found the same result of this fusion and exchange of cellular material, which has been found to increase metastasis. For example [93], found that human hepatocellular carcinoma cells with a low metastatic potential exhibit a significantly increased metastatic potential following fusion with BMSCs *in vitro* and in xenograft studies. Thus, the BMSCs and their molecules/exosomes, having been conditioned by tumor cells, were found to increase the probability of cancer in human patients [94]. Another potential problem with BMSCs is that T cells migrate into bone marrow and skew hematopoietic stem and progenitor cells towards myeloid lineages that augment inflammatory brain injury [95]. In other words, T-cells recirculate to bone marrow and condition cells in the BM to an inflammatory phenotype. Whether this occurs in mesenchymal stem cells in the BM is yet to be determined. The various phenotypes of BMSCs, including the cancerous phenotypes are difficult to distinguish [96]. In contrast, even ADSCs derived from cancer patients have been found to be safe for therapeutic development [97].

One of many reasons why ADSCs are preferred compared to BMSCs is that ADSCs express a low level of major histocompatibility complex (MHC) class I molecules and do not express MHC class II and costimulatory molecules. Even the exosomes of BMSCs express MHC class II proteins [98]. These problems in BMSCs are amplified when using donor, allogeneic BMSCs that have been replicated many times, essentially aging the cells, during expansion to develop the therapeutic. This is in contradistinction to ADSCs. Critically, when comparing experimental data of BMSCs to ADSCs from the same human donor, "ADSCs have a "younger" phenotype," according to stem cell scientists [99]. Indeed, Burrow et al. found that BMSCs have, among other negative attributes compared to ADSCs, an increased level of senescence compared to matched ADSCs. Senescent cells develop the senescence-associated secretory phenotype (SASP), a pro-inflammatory set of molecules where the local tissue effects of a SASP or specific SASP components have been found to be involved in a wide variety of age-related pathologies in vivo such as hyperplastic diseases, including cancer [100]. Whereas the use of BMSC transplants has a history of medical adverse events, including the induction of cancer in the recipient [51], fat grafting, along with its constituent ADSCs, have a long history of safety in medical procedures dating back to1893 when the German surgeon Gustav Neuber transplanted adipose tissue from the arm to the orbit of the eye in an autologous procedure to fill the depressed space resulting from a postinfectious scar [101]. Fat grafting's long history of being safe, regardless of the harvesting techniques used in patients [102] has been recently reviewed by physician-scientists at Baylor College of Medicine [103]. Furthermore, physician-scientists at Stanford University School of Medicine have favorably reviewed the safety and efficacy of using ADSCs to augment the outcomes of autologous fat transfers [104]. [105] have found that ADSCs and fat grafting for treating breast cancer-related lymphedema is safe and efficacious during a one year follow-on, where patient-reported outcomes improved significantly with time. In a randomized, comparator-controlled, single-blind, parallel-group, multicenter study in which patients with diabetic foot ulcers were recruited consecutively from four centers, ADSCs in a hydrogel was compared to hydrogel control. Complete wound closure was achieved for 73% in the treatment group and 47% in the control group at week 8. Complete wound closure was achieved for 82% in the treatment group and 53% in the control group at week 12. The Kaplan-Meier (a non-parametric statistic used for small samples or for data without a normal distribution) median times to complete closure were 28.5 and 63.0 days for the treatment group and the control group, respectively [106]. Treatment of patients undergoing radiotherapy with adult ADSCs from lipoaspirate were followed for 31 months and patients with "otherwise untreatable patients exhibiting initial irreversible functional damage" were found to have systematic improvement or remission of symptoms in all of those evaluated [107]. In animal models with a full thickness skin wound, administration of ADSCs, either intravenously, intramuscularly, or topically, accelerates wound healing, with more rapid reepithelialization and increased granulation tissue formation [108], and topically applied the ADSCs improved skin wound healing by reducing inflammation through the induction of macrophage polarization from a pro-inflammatory (M1) to a pro-repair (M2) phenotype [109]. Further, tumor-associated autoantibodies (TA) have been discovered in early- and late-stage disease for many human malignancies [110]. These TAs may exacerbate oncogenesis by disrupting the immune system. ADSCs have been shown to limit B cell mediated autoimmunity [111] and reduce autoantibody levels in serum [112], potentially reducing the potential for oncogenesis and metastasis.

In conclusion, microneedling, even with the shortest available needles, results in damage to the epidermis and dermis, thereby inducing an innate and adaptive proinflammatory immune response, including cellular proliferation. The use of topically applied bone marrow mesenchymal stem cell cytokines also induces an inflammatory innate and adaptive inflammatory state, and proliferation. Chronic inflammation in the skin, even when limited to only the epidermis, will induce system inflammation as measured in the circulation. While microneedling can be an important procedure for scar removal [113] and hair regrowth [114], for example, repetitive microneedling combined with bone marrow mesenchymal stem cell cytokine application will induce chronic inflammation and chronic wounding, a condition similar to the state of cancer [74,75,115–117].

Declaration of competing interest

Dr. Maguire has equity in NeoGenesis Inc.

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