The Role of B Cells in Skin Inflammation

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ABSTRACT

The role of B cells in skin inflammation highlights the versatility of B cells in their response to diverse immune stimuli perceived as external threats to the host. B cells play a vital role in the immune system's ability to effectively respond to offenses to the healthy skin microenvironment, such as wounds, malignant tumors, vector (tick)-borne pathogens, and the development of red meat allergies after a tick bite. Select examples from the literature that illustrate the role of B cells in these disrupted states reviewed individually below, and highlight little overlap in the role B cells play in the different diseases. Future studies will need to continue to research the relatively newfound role of B cells in maintaining healthy skin.

Introduction

The skin is a dynamic barrier organ that is instrumental in protecting the body from the outside environment. The skin has three main layers, the epidermis, dermis, and subcutaneous [1]. The epidermis is the top, visible layer of the skin. It is very porous and constantly shedding dead skin cells and replacing them with new healthy ones. The dermis is the second layer. It is thicker than the epidermis and highly vascular, comprising connective tissue interspersed with sweat and oil glands, nerve endings, and blood vessels [1]. The dermis is important in supporting the overall structure of the skin. The subcutaneous layer beneath the dermis provides insulation for the body and serves as a cushion to protect vital organs [1]. The skin is also inhabited by various microbes, including bacteria, fungi, and viruses, that interact with each other and make up the skin's microbiome [1].

B cells have an important role in maintaining homeostasis in healthy skin. B lymphocytes produce antibodies, which are made up of heavy and light chain proteins formed by gene rearrangements evolving during B cell development. These antibodies are displayed on their surface as receptors that allow them to proliferate upon exposure to both self and foreign antigens they may encounter. Before activation by antigens, B cells express receptors of the immunoglobulin M (IgM) class whereas activated B cells undergo further B cell receptor gene rearrangements that encode for IgA, IgG or IgE molecules. Activated B cells can differentiate into plasma cells, which are cellular factories for secreting these diverse antibody classes, including IgG, IgA and IgM.

B cells reside in the healthy skin of mammals and serve as first lines of defense against microorganisms. In human skin, B cells localize to the dermis where they are sparsely scattered during homeostasis [2]. The most prominent antibody that circulates in healthy skin is IgA [2]. IgA, along with a smaller presence of IgM, is found in human sebaceous and sweat glands [3]. IgA interacts with microbial antigens and plays an important role in the inactivation of viruses, bacteria, and other microbes in the skin and mucous membranes [4]. In the skin, IgA-mediated immunity occurs in both pilosebaceous regions and in sweat glands. In the pilosebaceous region, microbes reside in abundance and these organisms are held at bay below the mouth of the sebaceous duct by the immune system [4]. There is immunohistochemical demonstration of IgA in human sebaceous and sweat glands [4]. Tracer particles used to detect IgA were found in the interstitium near the epithelium and on basal and partly on lateral plasma membranes of columnar cells in skin tissue [4]. IgA antibodies work to prevent any possibility of infection by inhibiting the adhesion and/or

penetration of microbes that may be residing in sweat glands, and are most useful in warding off microorganisms already at the surface [4]. Specifically, from a study using light microscopy, IgA was found to be immunoreactive at eccrine sweat glands, which open directly into the surface of the skin, with much less presence in apocrine sweat glands, which open directly into the hair follicle [3]. If the B cells and other cells in the skin fail to control the invading microbe, then a stronger inflammatory response will develop.

In addition to keeping the cutaneous microbiome in check, B cells play an important role in the immune response to skin inflammation. Inflammation is a complex biological process caused by the body's response to stimuli it perceives as harmful. An immune response is a vital protective measure that causes and mediates inflammation. Thus, skin inflammation is a natural part of the body's response to a foreign substance. An inflammatory environment, specific to the agent invoking the immune response, is created and involves different types of recruited cells that both eliminate the foreign antigens and work to heal the inflamed region. B cells, in particular, play an important role in the immune response at inflamed portions of the skin by exhibiting protective and regulatory functions [5]. They have an inherent propensity to migrate toward inflamed sites of the skin [5]. In the broader scope of the immune response, the function of B cells is to recognize pathogens, process/present antigens, and produce antibodies. Once antibodies are secreted, they augment the ability of macrophages to recognize and degrade the antigen thus increasing antigen presentation on MHC II molecules. This leads to stronger activation of T cells that secrete growth factors that are essential to the division of immune cells, including B cells and killer T cells.

In this paper, the role of B cells in skin inflammation is explored using specific studies from the literature. In particular, this paper reviews the roles that B cells play in responding to wounds, malignant tumors, vector-borne pathogens, and development of red meat allergies after a tick bite.

B cells in Response to Inflamed Skin Lesions and Wounds

B cells play an instrumental role in healing inflamed skin lesions and wounds. In these conditions, the main responsibilities that B cells have are to promote the regeneration of tissues, including blood vessels and nerve fibers, to enhance cell proliferation, and to produce antibodies that bind to wounded tissue and facilitate the remodeling of damaged tissue by macrophages [6].

Chronic skin lesions affect 12–15% of patients with diabetes [6]. In a study performed in diabetic mice to examine the presence of B cells at skin lesions, it was found that the progression of wound healing in the skin was positively impacted by manipulating the balance of mature immune cell populations within the wound microenvironment through topical application of purified B cells [6]. Wounds that were treated with B cells developed much healthier skin at the wounds, as evidenced by a significant reduction in scar size, increased collagen deposition and maturation, enhanced angiogenesis, and increased nerve growth into and under the healing wound when compared to controls [6]. Likewise, the ability of B cells to hasten the regeneration of scarred skin tissue was demonstrated by live B cell treatment accelerating wound closure by approximately 3 days, performing significantly better than either equivalent numbers of lysed B cells or saline control [6]. With B cell treatment, collagen fibers were deposited in a pattern bearing greater similarity to normal skin in the scars of the wounds in comparison to ineffective large bundles observed in controls [6]. Collagen maturation was visibly improved in that the patterning of collagen fibers came to resemble intact skin with reduced scarring [6]. Improved angiogenesis and nerve growth proximal to the wound was also seen after topical B cell application, showing how B cells are vital for the regeneration of the wounded skin's microenvironment. B cells indirectly support angiogenesis by inducing the secretion of cytokines and growth factors in neighboring skin fibroblasts and keratinocytes [6]. Also, nerve endings that were repaired with B cell treatment increased expression of markers of axonal regeneration, such as GAP43 [6]. These findings support future studies that may lead to the development of a novel B cell-based immunotherapy to promote wound healing [6].

A second mechanism by which B cells accelerate the healing process at infected acute and chronic diabetic skin lesions is by enhancing cell proliferation. B cell treatment recruited different cells to the inflamed site that contributed to proliferation of cells that repair wounds [6]. The net addition of neutrophils and mitotic (dividing) cells such as

fibroblasts at the infected site contributed to the acceleration of the healing process, demonstrated by changes in wound morphology. After B cell application, there was much more migration of cells to the edges of the treated wounds and the wound edge morphology changed from round to flat, creating an epithelial tongue and a diminution in cell death as evidenced by less apoptosis around these edges [6]. The mitotic fibroblasts were in close proximity to B cells. Moreover, B cell treatment led to increased neutrophil presence at wound sites; neutrophils are an important mediator in the immune response and promote wound healing. After one day of B cell treatment, the number of neutrophils increased 45-fold and their rate of decline reduced by two and one-half fold, providing evidence that B cell treatment promotes this aspect of wound healing [6].

B cells also work to repair wounds in normal, non-diabetic conditions by producing IgG1 antibodies, which bind to antigens and facilitate their recognition by phagocytes, a process called opsonization. These antibodies bind to wounded tissue and enhance cutaneous wound healing by opsonizing dead cells and facilitating the engulfment of damaged tissue by macrophages [4]. In one study, splenectomies were performed on experimentally wounded mice to explore the role of splenic B cells in wound repair. Splenectomized mice demonstrated a delay in wound healing [4]. Treatment of these mice with naïve B cells rescued the delay in wound healing. These B cells produced IgG1 antibodies that bound to self-antigens expressed by wounded tissues [4]. These antibodies induced phagocytosis by activating Fc-gamma receptors present on neutrophils and macrophages, which facilitated the engulfment of dead tissues and enabled repair of the wounds [4].

B cells in Response to Melanoma

Melanoma is the most dangerous form of skin cancer. It is cancer of the melanocyte, the cell that produces pigment in the skin. The body's response to melanoma involves both an inflamed and immunosuppressed tumor microenvironment [7]. Tumor associated B cells (TAB) play a complex role fighting against melanoma [7]. TAB serve both a pro-inflammatory role that leads to tumor reduction but can also exert an anti-inflammatory role that leads to tumor progression.

In countering tumor progression and increasing patient survival, TAB sustain tumor inflammation as part of the immune system's response to the cancer. TAB are integral in skin inflammation and that, as part of the immune response, proteins secreted by human melanoma cells (also called secretomes) induce Nuclear Factor Kappa B (NF-kB) activation in TAB [7]. When B cells were exposed in vitro to the culture medium in which melanoma cells had been grown, they upregulated certain inflammation pathways, most notably tumor necrosis factor (TNF) signaling via NF-kB [7]. This upregulation enhances the inflammatory and immune responsiveness of TAB in the tumor microenvironment [7].

There is a subpopulation of TAB known as the tumor-induced plasmablast-like enriched B-cells (TIPB) that is clinically important to sustaining tumor inflammation in skin cancer [7]. Melanoma secretomes induce TIPB, which correlates with tumor inflammation and patient survival [7]. TIPB are necessary for sustaining the immune system response to tumors and for recruiting CD8+ T cells to fight human melanoma [7]. Local skin inflammation is promoted by functions of the TIPB, such as antigen presentation, T cell activation, and cytokine production. High and low levels of TIPB are associated with high and low levels of patient survival, respectively. High levels of TIPB led to 70% of patients surviving over 1500 weeks, while low levels of TIPB showed a tremendous, consistent trend downwards for patient survival, leading to 10% of patients surviving after 1500 weeks [7]. Thus, an ample number of B-cells from the TIPB must be present in the tumor microenvironment to sustain tumor inflammation so the patient can survive and fight off melanoma.

The loss of TAB in the tumor microenvironment leads to reduced melanoma-associated inflammation that is necessary to fight malignant skin tumors. When there is less TAB presence, there is a downregulation of necessary T cells and macrophages at the tumor microenvironment [7]. One study showed how B cells are required for optimal T cell activation [8]. By experimentally reducing B cell numbers at the tumor site, there was a significant impairment in the induction of CD4+ and CD8+ effector-memory T cells and inflammatory and cytotoxic cytokine-secreting T cells [8].

The depletion of B cells in the tumor microenvironment inhibited the collaborative effort of the immune system to fight melanoma since TAB bring all the moving parts together; when they are absent, there is extreme downregulation of essential cells.

TAB also serve anti-inflammatory roles with regards to tumor inflammation, allowing the tumor to experience uncontrolled growth in the body. In the microenvironment controlled by invasive tumors, the tumors promote the production of anti-inflammatory cytokines such as IL-10 by TAB [7]. Increasing levels of IL-10 in tumor tissues contribute to tumor progression. IL-10 has been shown to trigger a T helper 2 (Th2)-mediated immune response leading to the secretion of IgG4 antibodies [9]. IL-10 induced B cells in melanoma lesions to differentiate into IgG4+ B cells, which in the presence of the Th2 cytokine IL-4 produce IgG4 antibodies[9]. These antibodies contribute to counteracting antitumor immunity, since tumors experience unrestricted growth in the presence of IgG4 antibodies [9]. IgG4 antibodies also have antibody-neutralizing functions, such as inhibiting the functions of IgG1 opsonization of abnormal tumors cells, thereby allowing tumors to evade the attack by the beneficial humoral immune response in the tumor microenvironment [9]. The anti-inflammatory environment created by the IL-10 and Th2 B cells serves to suppress productive anti-tumor immune responses.

B cells in Response to Ixodes Ticks and Tick-Transmitted Pathogens

The role of B cells in the skin response to wounds and inflammation is also important in the case of blood-seeking arthropods such as Ixodes ticks and the pathogens these ticks can transmit. Ixodes ticks feed for several days and immunomodulate their skin site of feeding [10]. Both the act of tick feeding and the transmission of pathogens by the tick lead to the establishment of an inflammatory environment at the skin's surface. The actions of tick saliva on immune cells recruited to the bite site help tick-transmitted pathogens establish infection in the host [12].

Bioactive factors in tick saliva create a suitable microenvironment at the bite site that facilitate tick attachment and ingestion of the bloodmeal [12]. In the absence of ticks, the normal response to a skin wound involves hemostatic mechanisms to stop bleeding, which includes blood vessel vasoconstriction, platelet aggregation, and blood coagulation. Hemostasis also involves inflammation at the wound site and proliferation of leukocytes recruited to that site to prevent infection and to promote wound healing. In contrast, tick feeding suppresses normal wound healing responses like hemostasis [11]. The types of immune cells recruited to the site include epidermal Langerhans cells, keratinocytes, and phagocytes [10]. Specifically, phagocytes such as dermal macrophages, neutrophils and the "macrophage-like" Langerhans cells are essential for processing and presenting antigens to T lymphocytes and providing cytokine mediated co-stimulatory signals [12]. Tick-induced immunosuppression of the host is characterized by inhibiting primary antibody responses by B cells and also inhibiting T cells [13]. Tick saliva also polarizes the immune system toward down-regulating inflammatory cytokines [13]. Although ticks and their salivary components maintain an open wound in the host's skin during feeding, that wound is mostly healed when ticks complete feeding and detach from host skin [25]. There are important host proteins involved in this wound healing process that are taken up by ticks during the bloodmeal and re-secreted into the wound area. One of these proteins is the cytoskeletal protein actin, which was identified at high abundance in tick saliva and is associated with different aspects of wound healing [25]. Actin is essential in the cytoskeletal regulation of dermal regeneration [26]. Some actin proteins are positive regulators of wound healing while others are negative regulators. One negative regulator of wound healing is Flightless I (Flii), a member of the gelsolin family of actin remodeling proteins that has a role in inhibiting wound regeneration and repair [26]. Since Flii is an actin protein, it possible that it is present at the tick feeding site due to the strong presence of actin in the tick saliva that is secreted at the feeding site [25]. Topical application of Flii neutralizing monoclonal antibodies (FnABs) decrease Flii expression, which in turn results in improved wound healing [27]. The topical application of FnABs specifically accelerates re-epithelialization and improves the macroscopic appearance of early scars from wounds [27], similar to the effect seen with topical application of B cells. As described earlier, topical B cell treatment significantly reduced scar size, increased collagen deposition and maturation, enhanced angiogenesis, and increased nerve growth into and under the healing wound [6]. The intriguing finding is that these two different

methods, the topical application of FnABs to reduce the expression of the actin protein Flii and the topical application of B cells at skin lesions, both rely on B cells or their products and accelerate the wound healing process.

Ixodes ticks can transmit pathogens in their saliva to the bloodmeal host at the point of attachment on the skin. When a pathogen-infected tick attaches to a host and initiates feeding, the pathogen is transmitted via tick saliva to the host's skin within hours (viruses) to days (bacteria) of tick attachment. The three tick-transmitted pathogens that will be addressed in this paper are the two flaviviruses Tick-Borne Encephalitis virus (TBEV) and Powassan virus (POWV) and the bacterial agent of Lyme disease, *Borrelia burgdorferi*.

TBEV is a flavivirus found in Europe where *Ixodes ricinus* is the primary tick vector of this pathogen [10]. The role of B cells in skin inflammation in the immune response to TBEV is better understood than for other tick-transmitted viruses. One study concerning TBEV demonstrated the importance of localized skin infection in TBEV transmission to the bloodmeal host; the skin is also the site where ticks become infected when they feed on a viremic host [10]. The skin is the primary site of viral replication in the early phase of infection and is the first organ to initiate an immune response [10]. In experiments in mice, examination of excised skin from the feeding site, obtained 24 hours after tick attachment, revealed that epidermal Langerhans cells, dermal macrophages, and neutrophils migrated to the site of infection. It was determined that leukocytes and neutrophils composed the greatest number of migrators, while antigen presenting Langerhans cells were also present [10]. There were 10-100x more cells at the inflamed tick feeding site than at other distant sites of the skin, demonstrating the rapid and effective cell proliferation process as part of the skin immune response [10].

B cells play an important role in the body's innate and adaptive immune response to TBEV after the virus containing saliva is secreted into the skin [14]. Type I interferons (IFNs) mediate the skin's innate immune response to the bite by the infected tick by activating many proteins and cells as a first line of defense at the inflamed tick feeding site [14]. Importantly, these Type I IFNs promote B cell production of antibodies as part of the immune response [14]. B cells potentially play an immense role in preventing severe or fatal outcomes in the host by responding early at the inflamed tick feeding site. Langerhans cells and other dendritic cells from the skin can promote a systemic antibody response when they travel to the regional lymph nodes to present tick and TBEV antigens to B cells and T cells in lymph nodes. B cells multiply and begin to produce IgM antibodies and activated T cells incite B cells to also produce IgG, which are capable of entering tissues more readily than IgM. B cells that travel in the blood and into tissues, including the central nervous system, produce these antibodies, which can be detected in the serum and cerebrospinal fluid [14]. IgM antibodies are detected early in infection while IgG antibodies are more readily detected in the convalescent phase of the illness (~6 weeks); these TBEV-specific IgG antibodies confer life-long immunity [14]. B cells need to produce IgM and IgG for the systemic immune response since low concentrations of these neutralizing anti-TBEV antibodies in the serum results in high viremia and the possibility of severe TBE [14]. Although B cells are critical components of the immune response, this study did not specifically demonstrate when B cells produce antibodies at the tick bite site, leaving it up to inference that the proinflammatory environment at the site in the skin of the attached tick is eventually healed by the systemic immune response coordinated by Type I IFNs that began in the skin and lymph nodes.

Powassan virus (POWV) is another tick-borne flavivirus that can result in a severe neuroinvasive disease, with 50% of survivors displaying long-term neurological sequelae [15]. Human POWV cases have been documented in Canada, the United States, and Russia [15]. POWV is one of the lesser studied flaviviruses and little is known concerning the specific role of B cells at the inflammation site in the skin. Like TBEV, Ixodes ticks are vectors for POWV, and the virus is transmitted to a mammalian host very early in the tick feeding process. When a POWV-infected tick attaches to a host and initiates feeding, the virus is transmitted via tick saliva to the host's skin within 3 hours of tick attachment [15]. POWV entry into the host overwhelms the tick's effort to suppress the immune system, leading to an inflammatory immune response. After three hours of POWV-infected tick attachment and feeding, a complex pro-inflammatory environment is established that includes a significant upregulation of genes related to granulocyte recruitment, migration, and accumulation [15]. The study does not explain if and how this inflammatory response affects tick feeding or whether ticks feed to repletion when transmitting POWV.

Similar to examining cell recruitment in skin lesions and wounds, there is great cell proliferation in the pro-inflammatory environment at the tick bite site. Immune cells, including macrophages and fibroblasts, are recruited to the inflamed POWV-infected tick feeding site. The study examined the levels of cell infiltration at 3, 6, 12, and 24 hours post infection (hpi), and across all four time points the greatest level of cellular infiltrates was observed at the POWV-infected tick feeding site at 3 hpi [15]. The timing of the greatest amount of immune cell infiltration to the site of inflammation is the same length of time it takes for the tick to transmit the virus into the host's body. Although B cells were not analyzed in the study, there is large room for inquiry to be made concerning B cells in future studies based on the type of immune cells recruited to the pro-inflammatory environment at the skin's surface. Based on studies with TBEV, it is likely that the B cell antibody response plays a critical role in the outcome from infection. Also, as discussed earlier, B cells recruit mitotic fibroblasts to the site of inflammation in other acute skin lesions (e.g. diabetes) [15]. In wounds, B cells and macrophages work together in healing the injured site and clearing the site of dead cells [15]. Future studies may find an important role for B cells not only in deterring the virus but also in resolution of the inflammatory skin lesion, since B cells often work with fibroblasts and macrophages to resolve wounds.

Another tick-transmitted pathogen is the bacterial agent of Lyme disease, the most common tick-borne disease in the United States and Europe [16]. Lyme disease is caused by infection with Ixodes tick-transmitted spirochetal bacteria of the *B. burgdorferi* sensu lato complex [17]. Infection initiates when the bacterium enters the skin at the bite site, multiplying locally and causing a centrifugally spreading annular rash called erythema migrans (EM), which develops 7-14 days after the tick bite [17]. A recent study found that the median area of the inflamed EM lesion is 84.5 cm^2, with some patients having multiple lesions [16]. The skin's immune response in EM lesions attempts to eradicate the spirochete but if unsuccessful, spirochetes can disseminate to infect other organ systems, giving rise primarily to disease manifesting as multiple EM and/or cranial nerve palsies, meningitis, myocarditis or arthritis.

The EM lesion is the first manifestation of Lyme disease and is classically described on histopathology as a lesion consisting mainly of lymphocytes and macrophages in the dermis usually around blood vessels with smaller numbers of neutrophils [17, 18]. The dominant lymphocytes are T cells, whereas B cells are sparser in number. However, in larger lesions, which correspond to the duration of infection, the proportion of B cells increased in the cellular infiltrates [19]. B cells and the antibodies they produce are known to be important in preventing Lyme disease as well as in resolving disease manifestations [20]. The role of B cells in EM lesions has been poorly characterized to date. A recent study used single-cell 10X RNA sequencing to further analyze the immune cells in EM lesions, specifically focusing on the small population of B cells and their contribution to the immune response [28]. B cells in EM lesions were found to possess unique features such as preferential expression of IgM and gene expression patterns consistent with a role in local antigen presentation. These findings suggest that they are biologically very significant even though they are found in small numbers and newer technologies have permitted for the first time more in-depth studies of them.

Skin B cells in Allergic Responses to Ticks

A recent association has been made between the lone star tick *Amblyomma American* and development of allergies to red meat [21]. Red meat allergies pose serious acute health risks and can lead to severe reactions in the skin, GI tract, and respiratory system [9]. The allergic reactions are a result of the body becoming sensitized to a carbohydrate galactose-alpha-1,3-galactose (alpha-galactose) found in red meats. The carbohydrate is also found in Lone star ticks and introduction of this oligosaccharide into the skin induces B cell production of IgE antibodies to it [22]. Subsequently, consumption of dietary meats such as beef, pork, and lamb, which have high levels of alpha-galactose, can elicit a strong systemic allergic reaction and even anaphylaxis [9]. Lone star tick bites cause an allergy to red meat in 2-10 % percent of the general U.S. population [23].

One study delved into how cutaneous exposure to Lone Star tick bites promotes B cell production of antibodies and immune hypersensitivity [23]. The IgE-mediated immune response involves an overproduction of IgE that is detected in the serum and local inflammation of the skin [23]. The study used a mouse model to examine cells and

molecular pathways involved in the development of IgE antibodies after cutaneous exposure to tick proteins and alpha-galactose-containing beef thyroglobulin [23]. As mentioned above, tick feeding normally suppresses the local immune response. After the tick detaches, activated T and B cells then amplify the host inflammatory response by releasing specific cytokines and producing antibodies that target tick salivary/mouth-derived antigens [11]. The study found that mice could be sensitized to repeated exposure to subcutaneous injections of tick proteins and alpha-galactose and this led to detectable levels of IgE and IgG1 against these antigens in the blood. This required the presence of CD4+ T helper cells because depletion of this subset blunted the response. These listed observations of the skin further support the idea that local skin inflammation and B cells may help drive this response [23].

Studies of the allergy developed as a result of the Lone Star tick bite have focused on how cutaneous exposure to these tick bites elicits an inflammatory skin response [23]. Specifically, skin sections taken from mice in response to cutaneous tick exposure showed multiple signs of inflammation - dermal thickening, vasculitis and muscle fiber atrophy, and mixed inflammatory cell infiltration within the dermis and hypodermis, including granulocytes, lymphocytes, and B cells, and inflammation of the vasculature [23]. The physical signs of inflammation demonstrate the ability of ticks to modulate an aggressive allergenic immune response.

In the case of immune sensitization caused by the Lone Star tick bite, B cells are activated via Toll Like Receptors (TLRs) through a signaling pathway that involves the intracellular MyD88- signaling pathway. TLRs are a type of Pattern Recognition Receptor, which is a receptor class that functions to recognize Pathogen-associated Molecular Patterns (PAMPs). Specifically, TLRs are activated by many different pathogens including bacteria, virus, and fungi. B cells themselves express different TLR's and signaling through those receptors enhances antibody production. Furthermore, TLR signaling via the MyD88-dependent pathway in B cells is different in different contexts. For example, one compelling study demonstrated that IgG, an antibody produced in the MyD88-dependent allergenic antibody response, can alternatively serve protective functions for the skin during skin transplantations [24]. Notable effects of antibodies in skin graft regions include suppression of lymphocytes and increased levels of skin anti-inflammatory factors [24]. In the case of skin transplantation, during which something foreign is presented to the body, TLR signaling via the MyD88 dependent pathway in B cells suppresses an immune response [24]. In contrast, the immune system's response is opposite in the context of the tick bite by the Lone Star tick. Although something foreign is once again presented to the body and the immune system responds via the same TLR pathway, an opposite response occurs - immune sensitization.

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It is important to note that the immune sensitization caused by exposure to the tick bite is different than other skin allergenic responses such as contact hypersensitivity. The immune response to contact hypersensitivity does not involve TLR signaling via the MyD88-dependent pathway in B cells. Also, contact hypersensitivity occurs right on the skin surface and manifests in skin while the immune system response to the tick bite occurs in skin and manifests in the gut.

More research is necessary in order to understand why the immune system has an opposite response in two different contexts even though the response is through the same immune pathway. Although in the case of skin transplantation it is seen that antibodies suppress an immune response, this response is clearly opposite in the context of the tick bite-associated red meat allergy. Whether it be during an allergic response or skin transplantation, the studies above provide more evidence for the connection between the systemic B cell immune response and its versatile impact on inflamed skin.

Conclusion

This review describes the multiple and novel roles B cells play in the immune response to wounds, skin cancer (melanoma), tick feeding and tick-transmitted pathogens, and induction of red meat allergy after tick bite. The diversity of responses of B cells in these diseased states emphasizes that the role of B cells is dynamic and variable and assumptions cannot be made about other diseased states. Future studies will need to continue to research the expanding role of B cells in skin immune responses and studies summarized in this review may help inform those endeavors.

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