Cross-Reactive Inflammation to Milk as a Causal Factor in Acne

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Abstract

Milk consumption was linked to acne on and off for over a century in both the literature and common practice until the advent of tetracycline. During the past decade, milk, whey protein, and especially skim milk have again been linked to acne in a number of epidemiological studies and case reports. This association has been largely attributed to hormone content as well as to insulin increase, IGF-1 and the cascade of responses involving Fox01 and mTORC1 activation. Evidence has accumulated indicating that inflammation, rather than follicular plugging, is the initiating event in acne.

Based on clinical observation, research, and structural analogy, this article proposes that a specific food sensitization to milk peptide antigens induces a cross-reactive immune attack against the structurally similar structures of the PSFE apparatus inflamed in acne.

Acne due to food allergy results from incompletely digested food peptides leaking through a disrupted intestinal epithelial barrier and being recognized in the Peyer’s patches or transported to the PSFE unit as targets. Key to correcting this is improving digestive breakdown of milk proteins and reducing inflammatory elements in the gut microbiome with probiotics and other measures in order to heal this leakage.

While the literature has focused on C. acnes and its metabolites and TLR2 response as the main stimulus for the inflammation in acne, this article proposes that stimulation as an adjuvant effect or “danger signal” for the more specific and powerful adaptive immune response that causes the intense inflammatory response we recognize as acne. Scientific corroboration of this hypothesis would change the overall therapeutic approach to acne.

ABBREVIATIONS

P. Acnes: Propionibacterium Acnes; PSFE: Pilo Sebaceous Follicular Eccrine; TLR 2: Toll Like Receptor 2; NFKB: Nuclear Factor Kappa B; IGF1: Insulin Like Growth Factor 1; mTORC1: Mechanistic Target of Rapamycin Complex 1; FoxO1: Forkhead BoxO1; PPARy: Peroxisome Proliferator-Activated Receptor-γ; AKT: Protein Kinase B; CD 36: Fatty Acid translocase Cluster of Differentiation 36, SREBP-1C: Sterol Response Element Binding Protein-1C; RNA: Ribonucleic Acid; GI: Gastrointestinal.

INTRODUCTION

My hypothesis, that specific cross-reactive cellular immune attack is a key component causing the lymphocyte and neutrophil infiltrate key to formation of the acne lesion, is based on my research in cellular immune recognition and my three decades of experience in the practice of integrative dermatology. This hypothesis is important because it dictates a different approach for treating acne. I have found that correcting diet and adding supplements and probiotics to aid digestion [1] can serve to reduce the yeast population in the gut microbiome and fix leaky gut. Supplementing these eliminative and breakdown processes helps patients with acne who fail or reject conventional treatment [2,3].

Before the advent of antibiotics, elimination of milk from the diet was frequently prescribed for alleviating acne. After the availability of tetracycline, dermatologists found that it was much less traumatic to patients’ lifestyles to prescribe antibiotics to alleviate the acne rather than eliminate the dairy products that were such a large part of their diet.

While C Acnes and its metabolites may stimulate an immune response in the region of the PiloSebaceous Follicular Eccrine (PSFE) apparatus [4], they may also act as an immune adjuvant, enhancing, along with other non-specific and innate initiators such as TLR 2, the more specific attack on PSFE apparatus. Besides membrane bound immunoglobulin binding and antigen presentation, TLR signaling serves as the not the stimulus itself
but as the “danger signal” required to create the proper “context” for triggering a T cell response [5]."

I consider food allergy/inflammation to be a central mechanism initiating the inflammation in acne, and milk, for several different and interactive reasons, is especially likely to induce this inflammation [6]. Two main mechanisms are possible. Food-derived or other antigens or molecular modifiers could prime immune cells in the Peyer’s patches against themselves and cross-reactive targets in the follicular-sebaceous apparatus. Or escaping recognizable drugs, antigens and molecular targets could enter the blood stream and localize in the PSFE apparatus where they might serve as antigenic targets for cross-reactive attack [7,8].

Cross-reactive T cell reaction against milk products as a cause of acne is an important immune mechanism that is virtually absent from the dermatologic literature. Understanding how specific sensitization to milk can initiate the inflammatory response behind acne can help greatly when interpreting the events preceding an outbreak. This understanding can inform specific nutritional therapy to enhance the treatment of refractory acne patients, or those unwilling to use conventional medications. It is my hope to broaden the thinking and generate discussion about how this valuable food may cause issues in some individuals and to stimulate more detailed exploration of this complex relationship. Milk has numerous beneficial components and effects beyond protein, calorie, and growth promotion, including positive effects on brain development in neonates [9]. Milk is not the only food that can be a trigger or aggravator for acne in certain individuals, however this paper will demonstrate why it has a special status as a trigger.

In this era of recognition of biologic uniqueness, we have new appreciation of the contribution of epigenetic changes prompted by environmental exposures. With this in mind, it should be easier to see how different effects of milk could induce acne in different individuals, or that persons with acne could have a unique combinations of different effects from milk as part of their causative concert. I will outline some of the previously suspected mechanisms, and an important mechanism not widely discussed in the literature.

A number of studies have shown an association between skim milk and acne [10,11,12,13]. Danby has described how bovine hormones play a role in acne [14]. Others have discussed the contribution of lactose to increased glycemic index and consequent aggravation of acne, likely attributable to increasing insulin Insulin-like growth factor growth factor, which has definitely been linked to acne.

Most intriguing about these studies is the observation that skim milk was most associated with acne, rather than whole milk, which has a higher fat content. At first, anticipating that saturated milk fats might be contributory, this observation seems counterintuitive. But when the nature of the skim milk is scrutinized, one finds that extra milk protein is often added to produce a whiter, more milk-like product. So the actual milk protein is somehow suspect as a causative factor in acne. Let us consider how this could occur. Skim milk has a number of other characteristics compared to whole milk, including different spoilage characteristics [15].

There are additional studies showing that whey protein products used by body builders are associated with acne [16,17,18], that clears with their removal. As quoted by Melnik, Bulkley described exacerbation of acne by milk in 1,500 patients he studied, more than 130 years ago [19].

My interpretation is that some sort of sensitivity, or in the broadest sense, “food allergy” could be occurring in milk, thereby leading to inflammation of the sebaceous-follicular apparatus. I will discuss how this fits with the general concept of food allergy as it has emerged in the discipline now called functional medicine, and in addition, the specific nature of milk that makes it uniquely able to aggravate acne in some individuals. There is now evidence that cow’s milk protein peptides may be present in human breast milk where it could initiate sensitization [20,21].

The concept of “food allergy” is a reaction to specific foods with any variety of symptoms that may involve any organ system such as the gut or brain, beyond classical allergy symptoms. Any form of inflammation of the skin or other system is suspect. This goes far beyond IgE reactivity and may include any form of immune response including, delayed hypersensitivity, and recruitment of other cells such as neutrophils in the response as seen in acne. It presumes that there is exposure of the immune system to immunogenic moieties, so I will discuss how this can occur. An additional corollary of the concept of “food allergy” is that immune reactivity occurs against any food that is eaten repeatedly, such as milk, one of the most frequently consumed foods.

A number of other aberrant conditions must exist for epitopes from milk to cause acne by specific inflammatory attack. Gut barrier permeability issues have been widely discussed in inflammatory diseases and are also mentioned as a possible cause of acne [22]. Yeast overgrowth and an abnormal gut microbiome are likely to cause inflammation, which interrupts the gut endothelial layer, and allows translocation of immunologically recognizable peptides into the surrounding circulation and lymphoid tissue. A low sugar diet, probiotics, and anti-yeast supplements reduce this yeast-induced inflammation. The beneficial effect of the probiotic bacteria in yogurt restoring gut barrier function explains why some studies show that Lactobacillus containing yogurt does not lead to the increase in acne that milk does. It also may explain other studies showing that yogurt and milk both increase the incidence of acne [23]. Individuals with increased gut permeability caused by more than just yeast and aberrant bacteria might not improve permeability and react to similar milk antigens in both products.

There is more than one possible immunologic explanation of milk induced inflammation our expectation is that the digestive system breaks down proteins into small non-immunogenic amino acids, di and tri-peptides that can be absorbed across the gut barrier and distributed to the body through the bloodstream. Unfortunately, digestion is often incomplete, and larger immunogenic molecules persist.

How could these larger incompletely digested peptides trigger an immune response if they are in the small intestine, which has a barrier to prevent their escape. There would have to be a defect in the barrier allowing larger molecules to escape.
The first discussions of such a defective barrier came from well-respected scientists including W Allen Walker, who showed that large molecules of antigens or toxins could indeed cross the intestinal border in certain circumstances [24]. A limited literature existed under the rubric of “translocation” across the GI tract. More recently, this has morphed into the concept of “leaky gut”, expressing the defective nature of the gut barrier in some individuals allowing substances to leak out into the blood supply to the gut and into the surrounding lymphoid tissue around the small intestine known as the Peyers Patches. Thus we have the possibility of both sensitization of lymphocytes to milk or any other food allergens in the Peyers Patches, or the distribution of such antigens throughout the body via the blood supply.

The junctions between the epithelial cells forming the boundary in the small intestines have been shown to be relatively labile in response to a variety of influences, and appear to have a role in production of immune tolerance in the individual. For example, gluten has been shown to cause the release of zonulin, which breaks these junctional bonds [25]. Numerous other conditions can open these bonds including alcohol, gastrointestinal viruses, intestinal inflammation due to microorganisms or other causes, and even the presence of sensitizing food allergens inside the intestines. It can be deduced that progression of food allergies becomes a vicious cycle.

The clinical manifestations of “leaky gut” are gastrointestinal disturbances, and a variety of allergic or inflammatory sequelae after eating certain foods. With progression, it manifests as a reaction to frequently eaten foods and ultimately as a reaction to whatever is eaten. Also, it is worse after affected persons consume foods or medications that enhance extra-intestinal exposure to food or other gut antigens. Repeatedly, I see a decrease in intestinal symptoms such as bloating and bowel frequency associated with treatment to correct digestive issues preceding improvement of acne. So it can be seen how reaction to any number of foods or substances can set the stage for entry of milk or other food allergens into the circulation or immune recognition apparatus.

The understanding of the causes of acne has shifted. For decades, and even recently, plugging of the follicle due to desquamated cells, with subsequent backup of inflammatory fatty acids produced by P. acnes, was cited as the main cause [26,27]. P. acnes does appear to play a role in acne, most recently shown via TLR2 activation of NFKB [28]. However, the role of P. acnes as the initiator of either comedogenesis or the inflammation seen in acne has been questioned and must still be regarded as hypothetical [29]. More recent studies have shown that inflammation in the PSFE apparatus is the initial event, preceding the plugging [30,31]. Diet was generally considered unrelated to acne for several decades. Except for zinc and vitamin A, supplements were also considered unrelated.

More recently, sugar and hyperglycemic diets, and milk, especially skim milk, has been associated with acne. I agree with Melnik that the modern Western diet causes acne, and that people should switch to a Paleolithic diet, rich in vegetables and fish [32]. I will review the excellent literature and hypotheses Melnik and others use to explain the synergistic mechanisms at work in acne causation, and then go on to hypothesize important mechanisms he did not include. Melnik summarizes the effects of sugar on raising insulin levels, hence Insulin like growth factor (IGF-1), that is already elevated in teens. IGF1, along with branched chain and other amino acids activate the nuclear signal factor known as nutrient-sensitive kinase mechanistic target of rapamycin complex 1 (mTORC1), which increases anabolism and lipid production. He also argues that micro-RNAs in milk increase “a software delivering exosomal microRNAs, including microRNA-21 that enhances AKT–mTORC1 signal transduction”. IGF1 and insulin also depresses forkhead box 01 (Fox01) activity, causing an increase in the androgen receptor activity and peroxisome proliferator-activated receptor-γ (PPARγ). Depression of Fox01 also allows an increase of sterol response element binding protein-1c (SREBP-1c), which increases lipogenesis.

The aggravation of acne by a high glycemic diet can additionally be interpreted as aggravating yeast overgrowth in the GI tract [33], leading to gut barrier defects and escape of recognizable food, milk, and microbial antigens into the lymphatics and the blood.

Any food that causes food allergy can trigger acne, but why should skim milk or dairy products be especially prone to causing acne. Something is causing neutrophils and lymphocytes to accumulate around the PSFE apparatus in the acne lesion. Beyond the non-specific mechanisms initiating an inflammatory infiltrate, I hypothesize that there are specific mechanisms involving recognition and attack of epitopes in the PSFE apparatus.

Based on the studies I conducted with Levis on cross-reactive recognition by lymphocytes [34,35,36,37], I suspect that the likely candidate would be an analogous antigen to that found in the structure being attacked. The mammary glands of the cow have relatively analogous structure to the human breast, and there are structural similarities to apocrine glands and between those and the sebaceous glands hair follicles, and eccrine glands, and possibly between the secretions of these glands. Since cellular immune recognition requires strong binding of five of the 15 amino acids in each epitope [38], it is likely that structures with homologous or analogous derivation, function, proteins and receptors will share such amino acid sequences and hence antigenic similarity.

Similarities begin with embryogenesis, and “The embryonic mammary gland and hair follicle are both derived from the ventral ectoderm, and their development depends on a number of common fundamental developmental pathways” [39]. Milk secretion occurs by budding off from the apical side of the cells [40], of membrane-coated proteins from those cells, and has been called apocrine secretion [41]. The proteins are “either synthesized by the mammary cells or are transported by transcytosis from blood plasma” [42]. Therefore milk could contain either autologous proteins or ingested ones. There are significant differences in the literature on the nature on the nature of the mammary gland. Having already described it as being an apocrine gland, Jena calls it “an exocrine and sebaceous gland” [43] and shows eight proteins up-regulated during bovine lactation and 21 for water buffalo. Sebaceous carcinoma development of the breast has been reported in at least four
cases, again suggesting homology between the two glands [44]. There are antigens detected by new antibodies such as the CD 36/fatty acid translocase that are ubiquitous in the rat and notably are present in both the mammary and sebaceous glands [45]. Antibodies to rat caseins, one of the two major proteins in milk, have been detected in hair follicles and sebaceous glands [46]. It also has been demonstrated in ultracentrifuged goat milk, that actual fragments of mammary gland cytoplasm are present, yielding abundant possible epitopes for cross-reactive immune stimulation against analogous epitopes in the PSFE apparatus [47]. Finally, other factors that might stimulate immune recognition, such as tumor antigens, have been found in both sebaceous and mammary gland tissue in the mouse [48].

**DISCUSSION & CONCLUSION**

Milk is a product of the structure of other secretory mammary cells. So, in effect, when drinking milk, one is consuming structural elements of cells that are analogous on a biologic, morphologic, and likely immunologic level to the sebocytes lining the sebaceous glands, or elements of the hair follicle or eccrine ducts. Cross-reactive recognition and immune attack may be part responsible for the dense infiltrate around the sebaceous glands seen in acne.

Those people with inflammation of the small intestines are far more likely to have food allergens get across the intestinal barrier and cause acne, and milk is more likely to be an aggravating food because of the structural similarities mentioned, and because of the frequency of consumption. Leaky gut and inadequate digestion of proteins present in the milk and many other factors in the individual contribute to the set of circumstances leading toward inflammation, as evidenced by the fact that most people appear to tolerate milk without developing acne. Changes in the understanding of acne as an initially inflammatory process make this new perspective on its inflammatory etiology more relevant.

It is likely that acne is a spectrum of phenotypically related disorders produced by most of the mechanisms described in this review, including hyperglycemic diets leading to increased insulin and insulin-like growth factor, C. acnes, hyperlipemia, cell shedding leading to plugging, hormonal factors in the individual and diet, intestinal dysbiosis and leaky gut as well as exposure to food allergens, gut, and environmental toxins. The initial and later intense lymphocyte and neutrophil infiltrate may well be a result of not only P. acnes and innate immune response but also of the adaptive immune mechanisms such as TLR 2, but also of the adaptive immune responses they trigger. Those likely include cross-reactive immunity to epitopes either structurally located or deposited via the bloodstream in the PSFE apparatus. Specific immune attack of antigens in the region of the PSFE apparatus should be further explored experimentally as well as clinically to control this illness and is an early symptom of underlying dietary inflammatory and hyperglycemic dysfunction.

**ACKNOWLEDGEMENTS**

Barbara Wexler provided valuable help editing the text. No grants or other support was received.

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