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Acne: Transient Arrest in the Homeostatic Host–Microbiota Dialog?

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We propose that acne vulgaris represents a naturally developing, transient inflammatory interaction of adolescent facial skin with its new microbial/chemical milieu (*Cutibacterium acnes*, sebum), replacing a state of previous childhood skin homeostasis. This concept might explain why acne is characterized by strong regional and age specificity, prevalent occurrence, and resolution.

Inflammatory skin diseases (ISDs) are common, noncommunicable dermatoses that can diminish a patient's quality of life. Most ISDs affect specific skin regions, similar to the joint preference of rheumatic diseases [1]. Among ISDs, acne vulgaris can be considered a unique entity, due to the specific localization on sebaceous-gland-rich (SGR) skin regions and manifestation within a narrow age range associated with puberty [2]. Acne vulgaris occurs in 44–95% of teenagers of varying ethnicities, in contrast to the much lower frequency of other ISDs (e.g., psoriasis 2% and rosacea 2–10%) [2]. Furthermore, spontaneous remission of acne vulgaris occurs in up to 50% of affected patients, in contrast to other ISDs (e.g., psoriasis and rosacea), which have chronic intermittent courses [2].

To our knowledge, no ISDs, besides acne vulgaris, are characterized by both region and age specificity and such a high prevalence followed by frequent resolution. Thus, we posit that acne vulgaris might represent an individual ISD group. In light of new immunological and dermatological data, we propose a new concept for acne vulgaris pathogenesis, which might facilitate a better understanding of this disease leading to improved treatments. To simplify our hypothesis, we exclusively discuss teenage acne vulgaris (age 13–19 years).

All our barrier surfaces are inhabited by commensal microbes. The interactions between epithelial barriers and the microbiota are variable, within a spectrum ranging from mutualism to pure pathogenicity [3] (Table S1 in the supplemental information online). Initial colonization of our skin commences immediately after birth and the microbial communities become stabilized in the first years of life [4]. During this period, the skin immune system (SIS) evolves closely with microbes. This coevolution is essential for the education of the SIS, and the SIS can tolerate changes in microbiota populations during this time. In neonatal murine skin, this early tolerogenic period is mediated by the appearance of **regulatory T (Treg) cells** (see Glossary), as measured by flow cytometry [5]. Then, a homeostatic dialog between the microbiota and the developed SIS evolves – characteristic of most later periods of human life (childhood and adulthood). Controlled production of complement system components, antimicrobial peptides (AMPs), and interleukin (IL)-1 from keratinocytes and dendritic cells (DCs) are considered as important innate mediators of this symbiotic relationship [3]. Hair follicles can be recognized as special niches during this crosstalk, as they can preserve the steady-state by supporting the residency and recruitment of **Langerhans cells**, Treg cells, and by the reliance on **innate lymphoid cells** [6]. Follicles, covered by a thin epithelial layer compared to cornified multilayered interfollicular epithelium, can be considered as **locus minoris resistentiae** of the skin, which may explain its pivotal role in the host–microbe dialog. This homeostatic crosstalk may be impaired upon changes of the dialog partners.

During puberty, increased concentrations of androgenic hormones enhance sebaceous gland proliferation and sebum production. The greatest density of enlarged glands, and most sebum production, are found on the face, scalp, and upper back (SGR skin); therefore, a lipid-rich environment and a consequent shift in the skin microbiota occur in this area [4,7]. The new microbiota of SGR skin is characterized by an increased relative abundance of lipophilic *Cutibacterium* (e.g., *Cutibacterium acnes*) and *Corynebacterium* (e.g., *Corynebacterium simulans*) compared to childhood [4].

As shown in a murine model, even a short-term encounter with a new commensal on the skin can initiate a robust accumulation of effector T cells producing IL-17 and interferon (IFN)-γ as well [8]. Based on these data, we hypothesize that the sudden permanent changes in the microbiota composition of SGR skin during adolescence, which accompany increased sebum with its own inflammatory potential, may result in an inflammatory response, bypassing previous host–microbiota homeostatic crosstalk, and leading to acne manifestation. During this event, secretion of homeostatic mediators may increase in the skin, with keratinocytes and DCs producing increased concentrations of proinflammatory cytokines; this could lead to keratinocyte proliferation, the activation of **T helper (Th)17** and **Th1** cells, and the influx of neutrophils and macrophages. This shift from a homeostatic to an inflammatory state, could be initiated in follicles, resulting in follicular hyperkeratinization, closure of the **follicular infundibulum**, and **comedone** formation; these would be the first visible signs of acne, followed later by the

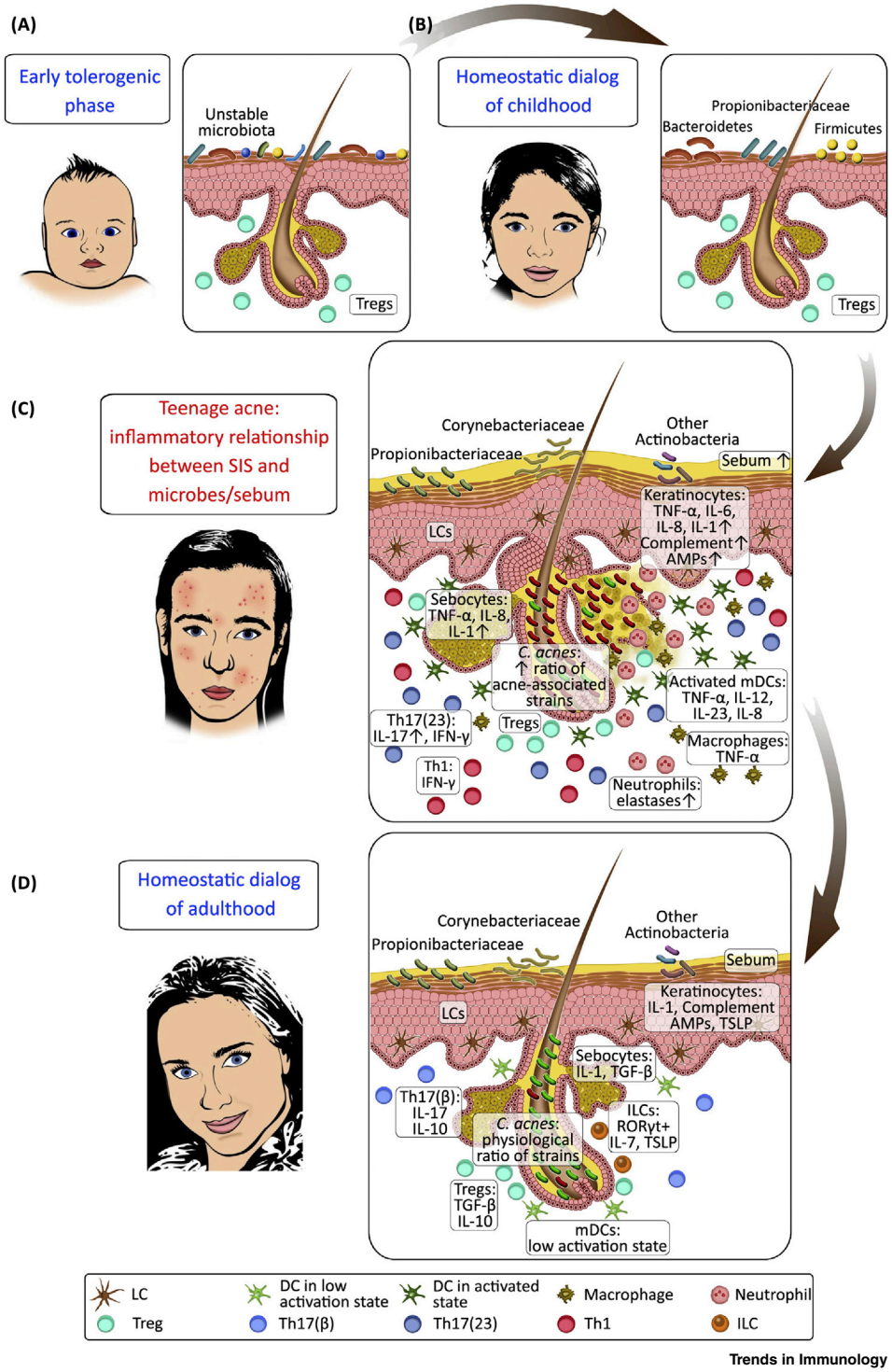

Figure 1. Model of Dynamic Interactions between the SIS and Its Microbial/Chemical Milieu in Human Facial Skin.

(A) Infancy: before the development of stabilized microbial communities, an early tolerogenic interaction between the maturing SIS and the microbiota is prevalent. (B) After this initial period, a homeostatic crosstalk evolves between the developed SIS and a childhood-type stable microbiota. (C) Adolescence: enhanced sebum secretion and shift in the microbiota composition (and probably other uncovered events, e.g., barrier breach) might

(Figure legend continued at the bottom of the next page.)

appearance of **papules**, **pustules**, and **nodules** (Figure 1).

This hypothesis is supported by mRNA data demonstrating that cytokines that are also characteristic of homeostatic host–microbiota dialog (transcripts encoding IL-1α and β, IL-10, AMPs, and IL-17) are increased in acne lesions, and promote inflammation together with newly produced inflammatory mediators [IL-6, IL-12, IL-23, tumor necrosis factor (TNF)-α, IFN-γ], relative to healthy skin [9]. Furthermore, *C. acnes* is capable of inducing both homeostatic and inflammatory states *in vitro*. In response to *C. acnes*, human keratinocytes, sebocytes, and mononuclear cells produce IL-1β, IL-10, AMPs, IL-17, IL-6, IL-12, TNF-α, and IFN-γ [10]. Further work using fluorescent microscopy confirmed that acne development was associated with the presence of *C. acnes* and its biofilm formation in skin samples from human subjects, while disease severity correlated with *C. acnes* lipase activity in acne lesions [11,12]. Moreover, *C. acnes* is characterized by high phenotypic variability and *C. acnes* strains associated with acne (e.g., HL110PA1 and HL096PA1) are capable of inducing inflammatory IL-17/IL-IFN-γ-producing $CD4^+$ T cells; by contrast, other *C. acnes* strains associated with healthy skin (e.g., HL042PA3 and HL110PA4) promoted protective IL-17/IL-10-producing Th cell phenotypes, as evidenced from flow cytometry and ELISA data [13].

The presence of high sebum production in teenagers seems to be essential for the otherwise commensal *C. acnes* community to exert its capacity of initiating inflammation. The highest secretion rate of sebum occurs during adolescence, declining even in post-adolescence and throughout [7]. Moreover, the sebum composition is altered in acne, and sebum concentrations correlate with disease severity [2]. Sebum can potentiate the propagation of *C. acnes* strains and can induce inflammation and follicular hyperkeratinization [2]. Indeed, others have referred to sebum as the 'fuel of the acne flame'. Thus, we posit that sebum might play a predominant role in driving the shift from homeostasis to inflammation. In the presence of *C. acnes*, human macrophages treated *in vitro* with different sebum components (e.g., palmitic and oleic acid) secrete significantly elevated concentrations of IL-1β and TNF-α, relative to controls, as shown by ELISA [14]. Hence, the extent or quality of the interactions between *C. acnes* and SGR skin may be modulated by sebum.

We posit that acne is a naturally occurring transient arrest of a homeostatic host–microbe dialog on SGR skin during adolescence. Part of our hypothesis is that the SIS tries to re-establish homeostasis again in post-adolescence, recognizing (tolerizing) the renewed microbial/sebum milieu as harmless. This might lead to the spontaneous resolution of acne. Multiple events (reduced sebum, compositional changes in *C. acnes* strains, regulation of SIS, and improved barrier integrity, among others) could influence the time of acne resolution, but this needs to be robustly assessed.

Genome-wide association data, primarily in adolescents and young adults with severe acne relative to controls, indicate that polymorphisms in inflammatory genes (e.g., *TNFA*, *IL1A*, and *IL6*), and also genes playing a role in the initiation of tolerance (*DBB2*, *TGFB2*, *OVOL1*, *SELL*, *TP63*, and *FST*), have been associated with disease manifestation [15]. Moreover, immunohistochemistry has revealed increased numbers of noninflammatory Th17 cells, nonactivated DCs, and Treg cells, along with thymic stromal lymphopoietin (TSLP) expression, and a IL-17/IL-10-positive cytokine milieu in adult SGR skin, compared to other skin regions (e.g., sebaceous gland poor) [16]. These unique features of SGR regions might potentially represent remnants of previous inflammation and acne, and a subsequent inflammatory resolution [16] (Figure 1).

In summary, we propose that the development of acne vulgaris is driven by dynamic changes in the interactions between adolescent SGR skin and its microbial/chemical milieu relative to childhood. This, in turn, might lead to a state of transient inflammation, rather

contribute to a dynamic change in the communication between the SIS and the microbiota in the skin, leading to inflammatory interactions. Cytokines associated with a homeostatic dialog may become highly increased in acne lesions (relative to non-lesions), promoting inflammation together with newly secreted proinflammatory mediators (depicted here) produced by keratinocytes, dendritic cells (DCs), and subsequently, infiltrating inflammatory T helper (Th)1 and Th17(23) (for IL-23) cells, neutrophils, and macrophages. These mediators initiate follicular hyperkeratinization, closure of the follicular infundibulum, comedone formation, and the development of acne papules, pustules, and nodules. The extent and time course of inflammation can vary across a wide spectrum among teenagers. (D) Following the resolution of acne, in adult SGR skin, under steady-state, SIS and region-specific microbes carry on a homeostatic dialog with the microbiota again, mediated by the controlled production of innate immune-cell-derived factors, including complement components, AMPs, IL-1, TSLP, and IL-7. Hair follicles may play a pivotal role in this crosstalk, supporting the residency and recruitment of LCs, Tregs, ILCs, as well as nonpathogenic Th17(β) cells to maintain homeostasis. Upward arrows depict increases (expression, concentrations, and ratios). *Propionibacterium acnes* (propionibacteriaceae) = *Cutibacterium acnes*. Other relevant bacterial genera are noted in the schematic. Abbreviations: AMP, antimicrobial peptide; IL, interleukin; ILC, innate lymphoid cell; LC, Langerhans cell; mDC, myeloid dendritic cell; RORγt, RAR-related orphan receptor γt; SGR, sebaceous gland rich; SIS, skin immune system; TGF, transforming growth factor; Th, T helper; Treg, regulatory T cell; TSLP, thymic stromal lymphopoietin.

than homeostasis. Presumably, this transition might be accepted as part of the physiological maturation of our SIS: a transient arrest in homeostasis (see Table S2 in the supplemental information online).

From a clinical perspective, although immune-mediated inflammation in acne is viewed as physiological, there is a high risk of permanent scar and pigment formation. Hence, patients may require specific treatments. Moreover, the mechanisms that initiate, amplify, resolve, or perpetuate acne might have common pathways with other organ systems, and the knowledge gained on a broader scale on this front might inform the potential development of improved treatments in acne.

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Glossary

Comedone: dilated infundibulum plugged by lipids and keratin. When the infundibulum is open to the skin surface, the lesion is called open comedone (black color is due to the oxidized sebaceous content). A closed infundibulum accumulating whitish keratin is referred to as a closed comedone.
Follicular infundibulum: upper part of the hair follicle that begins at the epidermal surface and extends to the opening of the sebaceous gland duct.
Innate lymphoid cell: immune cells that belong to the lymphoid lineage, defined by the absence of antigen specific B or T cell receptor; they have important functions in innate immunity against infectious microorganisms as well as in regulating inflammation and homeostasis.
Langerhans cells: dendritic antigen-processing and -presenting cells localized in the skin epidermis.
Locus minoris resistentiae: 'place of lesser resistance'. It refers to a body region that is more vulnerable than others, offering little resistance to microorganisms.
Nodule: (in skin): a solid, ellipsoidal, palpable lesion with a diameter >0.5 cm.
Papule: solid, elevated lesion <0.5 cm in size rising above the surrounding skin surface.
Pustule: circumscribed, projecting, pus-containing cavity in the infundibulum.
Regulatory T (Treg) cell: Foxp3-expressing subset of $CD4^+$ T cells; modulators of immunity, they maintain tolerance to self-antigens, and prevent autoimmune disease by potently downregulating or suppressing the induction and proliferation of effector T cells.
T helper 1 (Th1) lymphocyte: subset of $CD4^+$ T cells responsible for killing intracellular parasites and for perpetuating autoimmune responses. IFNγ is the main inflammatory cytokine produced by Th1 lymphocytes.
T helper 17 (Th17) lymphocyte: multifaceted IL-17-secreting T cell lineage with high plasticity, with physiological or pathological roles in at least three different levels. In healthy skin, they maintain homeostasis by supporting the integrity of the skin barrier by controlling commensal bacteria, inducing tight junctions, and expressing antimicrobial proteins They also protect barriers against pathogenic extracellular microorganisms, They are key players in the initiation and maintenance of inflammatory and autoimmune diseases. Th17 cells can be arbitrarily divided into non-pathogenic Th17(β) and pathogenic Th17(23) subtypes.

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