Jan D. Bos (1951-2020)

Menno de Rie, dermatoloog

Jan Dositheus Bos, geboren op 13 september 1951 in Leiden, studeerde geneeskunde in Rotterdam. Bos promoveerde in 1981 op een proefschrift over de immunologische aspecten van syfilis. Na de voltooiing van zijn opleiding werd hij als staflid verantwoordelijk voor de subafdeling Klinische Immunologie en Allergologie. Al op 39-jarige leeftijd volgde de benoeming tot hoogleraar in de Dermatologie en Venereologie en afdelingshoofd van de Afdeling Dermatologie van het AMC. Bos werkte nauw samen met professor Kapsenberg van de afdeling Celbiologie en Histologie van het AMC. Bos en Kapsenberg waren een van de eersten die de aanwezigheid en het belang van de T-cellen aantoonden in de normale en aangedane (psoriasis)huid, wat uiteindelijke leidde tot het concept 'Skin Immune System'. In 1990 verscheen het gelijknamige tekstboek. Bos bleef zijn hele werkzame leven betrokken bij het immunologisch onderzoek en de behandeling van psoriasis. Later in de jaren negentig kreeg hij ook belangstelling voor atopisch eczeem. Hij lanceerde de 'millennium criteria' en introduceerde het begrip atopiforme dermatitis.

Gedurende zijn carrière ontving hij vele onderscheidingen van buitenlandse dermatologische verenigingen: in Polen (1991), Hongarije (1992), Schotland (1996) en Duitsland (2001). Eervolle benoemingen bleven niet uit: Fellow of the Royal College of Physicians Edinburgh (FRCP Edin) en het Royal College of Physicians London (FRCP London). Daarnaast was hij visiting professor van de Universiteit van Michigan en de Massachusetts Medical School. Jan Bos was uitermate productief met ruim 330 publicaties en meer dan 50 promoties.

Jan Bos was een bijzondere man die wispelturig kon zijn. Hij nam geen blad voor de mond, wat niet altijd als prettig werd ervaren. Daarnaast kon hij ook uitermate charmant en behulpzaam zijn. In 2009 werd hij getroffen door kanker en in datzelfde jaar overleed zijn vrouw Anke. Deze schok kwam hij niet goed te boven waarna hij aftrad als afdelingshoofd in 2011. Aansluitend daarop kreeg hij de eervolle aanstelling als AMC-hoogleraar. In 2013 hertrouwde hij. Zijn laatste publieke optreden was op 15 december 2017 toen hij de Chanfleury-penning in ontvangst mocht nemen. Jan Bos stierf op 22 januari 2020, na een hersenbloeding.

review

The skin immune system: progress in cutaneous biology

Jan D. Bos and Martien L. Kapsenberg

The skin is an active, and in many ways unique, immunological microenvironment quite different from the other primary interfaces between the body and the environment (namely the mucosae). Here Jan D. Bos and Martien L. Kapsenberg identify the components of the skin immune system and describe the inflammatory and immunological responses that they can mount. New findings with regard to the immunophysiology and physiopathology of the human integument are emphasized.

The skin immune system (SIS) has been defined as the cutaneous complexity of interacting immune response-related cells[1]. Its cellular components, humoral factors and major pathological responses were recently reviewed[2], but several areas of interest emerged subsequently. These include the identification of keratinocytes as producers of a wide variety of cytokines upon nonspecific stimulation; the description of the 'dermal perivascular unit' as a major site of inflammatory and immunological reactivity; phenotypic and functional delineation of skin T cells, with new data pointing to the existence of skin seeking T cells; and a more precise definition of epidermal Langerhans cells as a unique subpopulation of antigen-presenting dendritic cells.

The concept of cutaneous immunobiology

According to Silverstein[3], Alexandre Besredka was first to point to the existence of organ-specific immunity, early in this century. While working in the Institut Pasteur with the cellular immunologist Ilya Metchnikoff, Besredka wrote at least two books on the subject[4,5]. In 1970, Fichtelius and co-workers published a classic but unconfirmed article in which they suggested the skin to be a first-level lymphoid organ, comparable to the primary lymphoid tissue thymus[6]. They referred to lymphoepithelial microorgans in the skin of newborns and human fetuses, which were detected at obvious and potential orifices of the body, such as under the nails, in the preputial fornix, in the fornix vaginae, at the conjunctival fold, around the glandular tissue of the external ear canal, around the pilosebaceous units of the lower ear lobes as well as scrotal skin, and around the primitive mammary gland tissue. These collections of lymphocytes were suggested to reflect lymphoid educational environments in which systemic immunity to exogenous agents was formed and in which cells were educated to discern self from nonself antigens. In adults, these lymphoid accumulations may recur and are then diagnosed as benign lymphoproliferative skin tumours (benign cutaneous lymphoma, lymphadenosis cutis benigna and many other variants). For dermatologists, this still forms a most attractive hypothesis as to the origin of certain rather common, nonmalignant ('reactive') lymphoid proliferative cutaneous diseases. However, the concept of the skin as a first-level lymphoid organ has not been substantiated.

Streilein subsequently defined the skin-associated lymphoid tissues (SALT) to include keratinocytes, the epidermally localized Langerhans cells (LCs) as antigen-presenting cells (APCs), the skin-seeking T cells (suspected to exist since the first observations on cutaneous T-cell malignancies), the endothelial cells of the skin (that direct the skin-seeking cells into the dermis), and the skin-draining lymph nodes, the latter being the site of induction of immunity by antigens that have been processed and transported by LCs[7,8]. Later, Streilein extended his concept of SALT by defining two subsystems, endoSALT and exoSALT[9]. In this subdivision, the dendritic epidermal TCR γδ-expressing T cells that have been identified in mice are crucial, but the human equivalent of this population has as yet not been identified.

In 1986, we proposed the term 'skin immune system' (SIS) which is now understood to describe the complexity of immune response-associated cells and humoral factors present in normal human skin. Table 1 summarizes the cellular and humoral constituents of the SIS.

Langerhans cells – unique dendritic cells

The term dendritic describes a number of different cell types that share a dendritic morphology. Apart from the dendrites of cutaneous nervous system cells, other cells of skin with a dendritic appearance include pigment forming melanocytes, Merkel cells (which possibly possess neuroendocrine functions), tissue macrophages, dermal dendrocytes, indeterminate cells: and LCs. In immunology, dendritic refers to a particular subset of APCs with wide distribution throughout the body. Steinman and Cohn[10] were the first to use the adjective dendritic to describe a cell population isolated from mouse spleens that had potent antigen-presenting capacity and a dendritic morphology *in vitro*.

It has been proposed that immune response-associated dendritic cells can be divided into three major subsets[11]: first, lymphoid dendritic cells – cells in

Table 1. Cellular and humoral constituents of SIS

Cellular	Humoral
Mainly related to innate immunity	
Keratinocytes	Fibrinolysins
Tissue macrophages	Antimicrobial peptides
Monocytes	Complement peptides
Granulocytes	Eicosanoids
Mast cells	Neuropeptides
	Cytokines
Mainly related to acquired immunity	
Langerhans cells	Secretory immunoglobulins
Tissue dendritic cells	Interleukins, interferons
T cells	Colony stimulating factors
Endothelial cells	Other cytokines (TGF, TNF)

lymphoid environments, such as interdigitating (reticulum) cells of lymph nodes and veiled cells in afferent lymph vessels. In the skin, these occur in certain types of relatively uncommon benign lymphocytic cutaneous tumours. Secondly, tissue dendritic cells – cells of connective tissue, including indeterminate cells and dermal dendrocytes. Third, given the unique position of similar cells in the stratified squamous epithelium of the epidermis, they are best described as epithelial dendritic cells, of which LCs are the major representative.

These dendritic cell subpopulations are thought to be interrelated and to represent various differentiation stages of one unique bone-marrow-derived cell line, which is closely related to cells of the monocyte–macrophage lineage. On the basis of observations in mice, Schuler and Steinman suggested that LCs might be precursors of lymphoid dendritic cells, since *in vitro* propagation was associated with a profound increase in antigen presenting and accessory functions, loss of some LC-specific markers, and expression of cell-surface antigens found on lymphoid dendritic cells[12]. They hypothesized that LCs might form the dormant pool of precursors of all dendritic cells of the body.

Table 2. Cytokines produced by human keratinocytes *in vitro*

Interleukins	IL-1α, IL-1β, IL-6, IL-8
Colony stimulating factors	IL-3, GM-CSF, G-CSF, M-CSF
Interferons	IFN-α, IFN-β
Tumour necrosis factors	TNF-α
Transforming growth factors	TGF-α, TGF-β
Growth factors	Platelet-derived growth factor, Fibroblast growth factor

IL-1: interleukin 1; GM-CSF: granulocyte–macrophage colony stimulating factor; G-CSF: granulocyte colony stimulating factor; M-CSF: monocyte colony stimulating factor; IFN: interferon; TNF: tumour necrosis factor; TGF: transforming growth factor. (Adapted from Ref. 15.)

The phenotypic transition of LCs in culture is accompanied by a remarkable change in function. Freshly isolated LCs are very efficient in processing intact proteins but are relatively poor presenters of the peptide fragments of these proteins; cultured LCs do not process efficiently but can present preprocessed proteins to T cells extremely well. These observations support the widely accepted sequence of events that LCs trap antigens in the epidermis, and carry the antigen to the draining lymph nodes where they present the peptide fragments, as lymphoid dendritic cells, to T cells. However, it might well be possible that the observed functional changes during *in vitro* propagation might be related to the recovery of LCs from the trypsinization procedure used during their preparation[13,14].

Cytokine production by keratinocytes

Together with the biochemical and biological definition of immunologically relevant autocrine, paracrine and exocrine proteins, such as interleukins (ILs), interferons (IFNs), colony stimulating factors (CSFs), tumour necrosis factors (TNFs), growth factors (GFs), and various other cytokines, it became apparent that the principal cell of the epidermis, the keratinocyte, could function as a major source of many of these molecules[15].

It was first notified that keratinocytes have immunological capability when various effects on maturation of T cells in coculture experiments were demonstrated. It was then discovered that keratinocytes phagocytose *in vitro*, and that the continuous uptake of melanosomes produced by epidermal melanocytes may be an *in vivo* equivalent of this. Keratinocytes have also been suggested to have accessory cell functions, perhaps even antigen-presenting capacity[16]. Gaspari *et al.*[17,18] have shown that hapten-modified MHC class II$^+$ keratinocytes may generate downregulating signals that can interfere with the induction of contact hypersensitivity.

The list of cytokines that keratinocytes are capable of secreting into the extracellular fluid of the epidermal compartment is impressive (Table 2). Most of these factors are not constitutively produced *in vivo*, but can be induced by a variety of nonspecific stimuli, including chemicals that induce irritant dermatitis, ultraviolet irradiation, tumour promoting agents, epithelial trauma, and other types of injury. It is possible, therefore, that keratinocytes are involved in many different inflammatory and immunological skin diseases, as nonspecific activators responding to a wide variety of injurious events. According to Barker *et al.*[19], keratinocytes act as pro-inflammatory signal transducers, responding to nonspecific external stimuli with the production of inflammatory cytokines, adhesion molecules, and chemotactic factors. In this way, the SIS is readied for specific immune reactions against (neo)-antigens produced in the initial, nonspecific, epidermal stimulation stage (Fig. 1). As described above, this nonspecific upregulating activity of keratinocytes may be accompanied by immunologically-specific downregulating effects on delayed-type hypersensitivity skin reactions.

The dermal perivascular unit

Histologically, the perivascular area of postcapillary venules of papillary dermis, deep dermis, and skin appendages contains the highest concentration of immune response-related cells of the integument. At these sites, close to the endothelial cells and pericytes of the vasculature, mast cells, monocytes and macrophages, and T cells are frequently present. In addition, tissue dendritic cells, which may be related to LCs, may be observed[20,21]. In many inflammatory skin diseases, these perivascular reactivity centres expand into perivascular cuffs. These are especially apparent in dermatological diseases, such as polymorphous light eruption, Jessner's lymphocytic infiltrate, morbilliform drug eruptions, cutaneous lupus erythematodes, erythema exsudativum multiforme, lymphocytic vasculitis, and others.

It might be argued that these reactivity centres, which contain all the elements necessary for a vigorous immune response, are not skin-specific. What discriminates them, however, is their close proximity to the epidermis, from which a large array of cytokines bombard these sites upon any epithelial injury. As a result, endothelial cells increase expression of the adhesion molecules necessary for leucocyte immigration from the circulation, as described above.

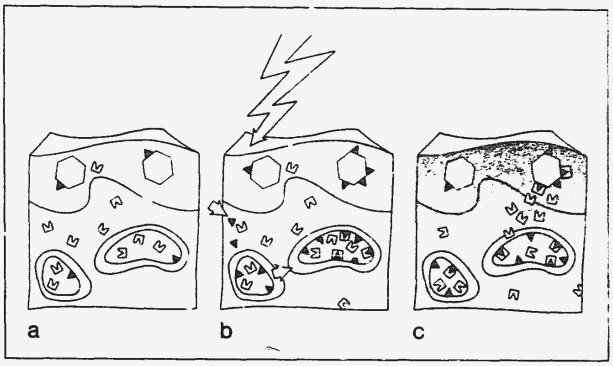

Fig. 1. *(a) The expression of adhesion molecules by keratinocytes and endothelial cells is low in normal human skin. (b) In the initial phase of non-specific cutaneous inflammation, which is initiated by non-specific stimuli (flash arrow), keratinocytes release IL-1 and TNF-α, and express ICAM-1. IL-1 and TNF-α activate dermal vascular endothelium, which upregulates expression of addressins (closed triangles) ICAM-1, E-selectin, and vascular cell adhesion molecule-1 (VCAM-1), some of which may become detectable in interstitial fluid or even in peripheral circulation (open arrow). These events allow adhesion of circulating leucocytes (open v-shaped figures), especially granulocytes and memory T cells to the dermal endothelium. (c) Concomitant keratinocyte secretion of IL-1 and IL-8 provide a chemotactic concentration gradient (shaded area), particularly for T cells inducing migration into the epidermis (modified from Barker* et al.[19]).

T cells of human skin

An essential feature of the SIS, the presence of substantial numbers of T cells in normal skin, was not appreciated until monoclonal antibodies (mAbs) enabled their detection and localization. The total number of T cells thus present in normal human skin is, in an adult, around 4 billion, over 90% of which are localized in the dermal perivascular units[22]. Immunophenotyping has revealed that a subset of these perivascular T cells is activated and that they are mainly of the memory phenotype[23].

In peripheral blood, a subset of T cells expresses cutaneous lymphocyte-associated antigen (CLA), as defined by the monoclonal antibody HECA-452 (Ref. 24). HECA-452 recognizes a 200 kDa cell surface glycoprotein which is present on approximately 16% of peripheral blood T cells. Over 85% of cutaneous inflammatory T cells from different dermatological diseases express HECA-452, as compared to less than 5% of T cells at uninvolved extracutaneous tissue sites. Subsequently, it was suggested that the counterstructure for this T-cell antigen may be associated with E-selectin (formerly known as endothelial cell leucocyte adhesion molecule-1 (ELAM-1))[25]. Thus, E-selectin may act as an adhesion molecule or vascular addressin for a specific subset of skin-homing memory T cells[26]. A precise study revealed that in normal human skin, 43% of T cells express CLA[27].

Epidermal T cells are a distinct component of the SIS. Following the recognition of the γδ T-cell receptor, it quickly became apparent that the epidermal dendritic cells previously observed in mouse epidermis expressed these receptors, as a result of which they were renamed dendritic epidermal T cells (DETCs)[28]. Human epidermal T cells, however, are not dendritic and the proportion of αβ and γδ T cells is not substantially different from that observed in normal human peripheral blood[29,30].

Immunophenotyping of the T cells of the integument is now being complemented by functional studies, especially in cutaneous disease. For example, T cells can be isolated from inflamed skin and cloned in an antigen-independent fashion by limiting dilution, and the antigen specificity, cytokine secretion profiles and cytolytic capacity studied in detail. By this method, it has been established that the T cells infiltrating the integument in allergic skin disorders, such as contact allergy and atopy, have distinct lymphokine secretion profiles[31–33].

Epilogue

Some of the most important functional features of SIS now recognized are summarized in Table 3. Many of these are unique to the skin. In addition to what is reviewed above, the nature of autoantigens involved in autoimmune bullous dermatoses, such as pemphigus and pemphigoid, have been identified. Also, the array of dermatological treatment modalities has been substantially extended with the introduction of new immunotherapies (cyclosporins, FK506, experimental monoclonal antibody immunotherapy, extracorporeal photopheresis) for the treatment of scleroderma, psoriasis, atopic dermatitis, pyoderma gangrenosum, lichen planus and many others.

Many of the skin-specific features of the SIS are related to its superficial location and the fact that it is continuously challenged with antigen. The skin shares its continuous exposition to exogenous antigens and infectious agents with the respiratory and gastrointestinal tracts. However, exposure to sun rays, especially ultraviolet irradiation, is unique and photoimmuno-

Table 3. Functional aspects of SIS

Continuous exposure to environmental agents, including biologically significant sun rays (photons), biochemically reactive toxins and antigens, and infectious agents
Epithelial pro-inflammatory response to various stimuli
Epithelial homing of dendritic cells (LCs)
Induction of primary immune responses to certain antigens, following migration of antigen-trapping APCs (LCs)
Expression of immunity to known antigens
Induction of tolerance to certain antigens
Continuous challenge by endogenous immune complexes
Endothelial cell-directed immune response amplification
Existence of recirculating pool of skin-specific T cells
Immunosurveillance in relation to tumour prevention
Known autoantigens mainly involved in cell–cell adhesion

APC: antigen presenting cell; LC: Langerhans cells.

dermatology forms an important area of research. In addition, a major difference between skin and the gastrointestinal tract is the lack of lymphoid tissue within the dermal stroma of the integument under physiological circumstances. As such, induction of immune responses does not normally occur within the skin itself. However, LCs have a significant role in the presentation of skin-derived antigens to the skin-draining lymphoid tissues.

The effector function of immune system in the skin is realized by a unique combination of pro-inflammatory, upregulating keratinocytes that prepare the dermal stroma for specific immunological activity, paralleled by a simultaneous increase in the migratory activity of antigen-trapping APCs (LCs) which induce expansion of specific lymphocytes in the skin-draining lymph nodes. These lymphocytes can then enter the skin as a result of the expression of skin-specific adhesion molecules that interact with their upregulated counterreceptors on the endothelial cells of the dermal perivascular units. Naturally, downregulation of inflammatory and immune activity must subsequently ensue, and keratinocytes may be involved in such a homeostatic process.

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