Cellular and Molecular Mechanisms in the Induction Phase of Contact Sensitivity

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Abstract
During the induction phase of contact sensitivity, hapten-specific Th1 cells are primed by epidermal Langerhans cells. These Langerhans cells present hapten on MHC class II molecules and provide costimulatory signals. This presentation discusses the induction of cytokines in Langerhans cells and keratinocytes by haptens and their regulatory effects on contact sensitivity. Haptens were painted on the skin of normal BALB/c mice and epidermal cells were prepared at various times thereafter. Langerhans cell-derived interleukin (IL)-1β mRNA was observed as early as 15 min after hapten painting. In keratinocytes, tumor necrosis factor-α, IL-1α, IP-10, MIP-2 and IL-10 were found to be up-regulated. IL-1β appeared to be a ‘master’ cytokine since it was able to mimic the effects of haptens, such as the increase of MHC class II expression in Langerhans cells and activation of the cytokine cascade. Injection of anti-IL-1β monoclonal antibody prior to hapten application completely prevented epicutaneous sensitization. In vivo application of IL-10 by intradermal injection prior to epicutaneous application of TNCB induced antigen-specific tolerance and impeded the induction of proinflammatory cytokines.

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Introduction
Contact sensitivity (CS) is a frequently observed inflammatory disease of the skin. The induction of CS in mice has served as a reliable and reproducible model for the in vivo induction of CS. Using this animal model it has been shown that Langerhans cells (LCs) as antigen-presenting cells and keratinocytes are intimately involved in this process. It has recently been suggested that contact allergens (haptens) are actively involved in T cell activation not only by providing signal one (recognition), but also by inducing important accessory functions in LCs, keratinocytes and endothelial cells [1]. Early after allergen application, endocytotic processes in LCs and MHC class II molecules are increased [2, 3] and the migration of LCs to the regional lymph nodes is enhanced. In this short review we will discuss the effects of haptens applied to the skin of nonsensitized mice on the induction of cytokines in the epidermis and the functional significance for the induction of CS.

Experimental Model
The experimental details are described in recent publications (4-7). Both sides of the ears of BALB/c mice were painted with either the contact sensitizers TNCB, DNFB, DNCB, the tolerogens DCNB or DNTB or the irritant SLS. Total epidermal mRNA was extracted and a sensitive reverse transcriptase-polymerase chain reaction (PCR) technique was used to quantitatively compare the regulation patterns.
of mRNAs specific for MHC class II complex I-A\textsubscript{α} or various cyto-kines (see below). For some cytokines, proteins or functional activities were detected in supernatants using ELISA or bioassays. For functional in vivo studies, mice were sensitized by painting one ear with the hapten. Five days later, a lower concentration of the hapten was painted onto the ear and ear thickness measured 24 h later. Student’s t test was used for statistical analysis.

Results and Discussion

Enhanced LC-derived interleukin (IL)-1ß mRNA signals were detected as early as 15 min after skin painting with allergens. MHC class II I-A\textsubscript{α} (LC-derived) and IL-1\textalpha, interferon (IFN)-inducing protein (IP-10), macrophage inflammatory protein-2 (MIP-2), tumor necrosis factor (TNF)-α, granulocyte/macrophage-colony-stimulating factor (all keratinocyte derived) and IFN-γ (Tcell derived) were enhanced by the hapten painting.

To assess the pathophysiological significance of LC-derived IL-1ß, the cytokine was injected locally into the ear skin and cytokine mRNA signals were assessed by quantitative reverse PCR transcriptase. IL-1ß caused a similar epidermal cytokine pattern as topical application of hapten including an enhancement of LC MHC class II expression. LCs derived from IL-1ß-injected skin were 2- to 3-fold more potent accessory cells in an anti-CD3 proliferation assay than LCs from IL-1ß- or sham-injected skin. Hamster anti-murine IL-1ß monoclonal antibody injected into the skin prior to TNCB treatment completely prevented sensitization to this allergen.

Contact allergens also increased IL-10 mRNA signals and IL-10 protein in keratinocytes, as detected by immunoprecipitation. IL-10 mRNA signals were enhanced 4 h after hapten application and were maximal after 12 h. Using soluble-protein-antigen-specific Tcell clones AE7 (Th1) and D10.G4 (Th2), a differential effect of IL-10 on Tcell activation was observed. IL-10-pretreated LCs were essentially unable to induce Th1 proliferation in response to native protein or peptide antigen, whereas LC-supported Th2 cell proliferation was unaffected [8]. Further studies showed that IL-10 probably down regulates the costimulatory signals required for the induction of Th1 cell proliferation, and that it had no effect on the MHC class II antigen expression on LCs.

In vivo studies showed that prior injection of IL-10 locally before application of the hapten induced a long-lasting hapten-specific tolerance which appeared to be due to an antigen-specific T cell anergy. To elucidate the mechanism of action of IL-10-induced unresponsiveness, the epidermal cytokine pattern was analyzed on the mRNA level after injection of IL-10 or controls and application of allergen. Injection of IL-10 (but not controls) significantly impeded the induction of the proinflammatory cytokines IL-1ß, TNF-α and IL-1α.

It is concluded from these studies that hapten-induced cytokines play an important role in the elicitation and regulation of CS response, and IL-1ß and IL-10 appear to be of major importance.

References


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