demonstrate that a significantly greater amount of TNF-α was released from mast cells of UVB-S mice compared to UVB-R mice.[18] Thus, we have tentatively concluded that mast cells are the immediate cutaneous source of TNF-α that impairs CH induction at the UVR site.

We next determined whether mast cells are also the cutaneous source of IL-10 that appears to be the primary mediator of the hapten-specific tolerance that follows application of hapten to the UVR exposed site.[16] Our suspicion of mast cells arose in part because the speed with which the IL-10 gene is activated in keratinocytes exposed to UVR is rather slow (after 6–8 hours), whereas hapten induces tolerance when applied to UVR-exposed skin within 30 minutes of UVR treatment. To this end, Alard and her colleagues[20] have reported that if cutaneous mast cells are loaded with IgE and then triggered with specific multivalent antigen, hapten application to the site leads to tolerance. Moreover, anti-IL-10 Ab abrogated tolerance induction that was elicited by multivalent antigen in IgE loaded skin. These findings indicate that triggering of mast cells *via* their receptor for IgE mimics the deleterious effect of UVR on cutaneous immunity, including the promotion of hapten-specific tolerance by an IL-10-dependent mechanism. To determine precisely if the source of IL-10 in these experiments is dermal mast cells, Alard *et al.* showed that acute, low-dose protocol of UVR exposures failed to induce tolerance in mast cell-deficient mice (Sl/Sl^d).[20] Very recently, Hart *et al.* have reported that the systemic tolerance induced by exposing mice to a single large dose of UVR requires the presence of mast cells.[21] In the aggregate, these data indicate that IL-10 is released from mast cells after UVR exposure, and that the release of this immunomodulatory cytokine promotes tolerance.

Nerve Endings as a New Member of SALT

Since UVR penetrates only into the epidermis and upper reaches of the dermis,[11] it is problematic that dermal mast cells prove to be the primary source of the immunomodulatory cytokines that alter cutaneous immunity after UVR. How can UVR trigger the release of TNF-α and IL-10 from dermal mast cells? The most likely mechanism involves another unsuspected player in the cutaneous immune cascade.

Several lines of recent inquiry have led investigators to consider a role for neuropeptides normally found in epidermal termini of c-type nerve fibers in cutaneous immunity of the CH type.[22] Although Paul Langerhans[3] originally proposed that LC themselves were components of the nervous system, their origins from hematopoietic progenitors has been clearly established.[23,24] Granstein and his colleagues[7] reawakened attention to the neural connectivity of LC by demonstrating that c-type nerve fiber termini containing CGRP were present on the surfaces of LC in normal skin. Asahina *et al.*[25] reported that CGRP was able to inhibit CH induction, and that CGRP was released from nerve fiber termini in rat skin exposed to UVR.[26] To complete this intriguing idea, Niizeki *et al.*[27] have recently demonstrated that an antagonist of CGRP can reverse the deleterious effects of acute, low dose UVR on CH induction. Moreover, CGRP was shown to impair CH induction *via* a TNF-α-dependent mechanism. Not surprisingly, both UVR and CGRP fail to impair CH induction in mast cell-deficient mice, but not in their wild type littermates.[19,27] These data suggest that UVR stimulates cutaneous nerve endings to release CGRP, and that CGRP in turn induces mast cells to secrete TNF-α, leading to impairment of CH induction. Thus, the link between UVR and dermal mast cells may be neuropeptides released from cutaneous nerve termini.

Since many nerve endings contain both CGRP and substance P (SP),[22] and since these neuropeptides often display antagonist functional properties, it is important to know the extent to which SP can modify cutaneous immunity. Several laboratories have inquired recently into the possible role of SP on the induction and expression phases of CH.[28–30] However, the results of the experiments failed to prove a role for SP in the induction phase of CH. Very recently, Niizeki and Streilein have investigated whether an agonist of SP can alter CH induction.[31] The results clearly indicate that SP agonist promotes CH induction in an almost "adjuvant" like effect, rendering subthreshold doses of hapten immunogenic. More important, SP agonist was able to reverse the effects of UVR on CH induction, rendering the mice able to develop intense CH.

The ability of SP agonist to reverse the deleterious effects of UVR on cutaneous immunity presents a paradox. Termini of c-type nerve fibers in the epidermis contain both CGRP and SP (reviewed in reference 22), and both are released following UVR exposure.[26] Yet, CGRP appears to dictate the immune outcome. As mentioned previously, CGRP plays a leading role after UVR in causing release of TNF-α, which in turn are the primary mediators of the immune deficits observed.[27] Since exogenous SP (SP agonist) reverses these UVR-dependent immune deficits, why doesn't SP neutralize the effects of CGRP when both are released by UVR exposure? The reason may rest with the stability of these two neuropeptides. Native SP has a very short half-life *in vivo*, presumably because it is readily degraded by endogenous neuropeptidases.[32] CGRP is much more stable, as is the SP agonist we used in our experiments. Thus, CGRP may dominate after UVR exposure simply because SP is rapidly degraded and unable to materially influence subsequent immune