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19 ABSTRACT (Continue on reverse if necessary and identify by block number) The skin is an organ which not only provides a cover for the body but also has an immunologic function. This project sought to determine whether stress plays a role in the susceptibility to infections. To do this we developed a method of isolating mRNA from keratinocytes grown in defined medium and from Langerhans cells (LC) maintained in serum containing medium. We have shown that keratinocytes demonstrate relatively large amounts of mRNA for interleukin-1 (IL-1) alpha; by contrast, LC express mainly mRNA for IL-1 beta and very little IL-1 alpha mRNA. Furthermore, we have demonstrated that both of these IL-1s do not stimulate keratinocyte growth. This is in contrast to reports in the literature. Finally, we have demonstrated that keratinocytes grown in defined medium, as well as, cells of a squamous cell carcinoma cell line express receptors for somatomedin-C/IGF-1 and for IGF-2 <u>in vitro</u> . Furthermore, the squamous cell carcinoma cells secrete binding proteins for these two peptides.			
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I. INTRODUCTION

The epidermis consists of 4 cell types, the melanocyte, Langerhans cell (LC), Merkel cell and keratinocytes in various stages of differentiation. The LC, first described in 1868, is a bone marrow derived immune competent cell which has properties of a tissue macrophage (Katz, et al, 1982). As would be expected for an immune competent cell, LCs express a number of cell surface markers, such as HLA-DR, Fc and C3 receptors, structures which play a role in the immune response (Rowden, et al, 1977; Stingl, et al, 1978). By contrast, expression of class I antigen by LC is diminished or entirely absent (Caughman, et al, 1986). Another cell surface antigen, OKT6, is demonstrated by LC and provides a convenient marker for this cell because the LC is the only cell in the epidermis to express this antigen (Fithian, et al, 1981). The only other cell which expresses OKT6 is the immature thymocyte and it is conceivable that LC are of T cell origin. Some of the cell surface markers expressed by LCs are decreased by a variety of in vivo treatments such as glucocorticosteroids, short wave length ultraviolet light and photochemotherapy using psoralen (PUVA) (Berman, et al, 1983; Nordlund, et al, 1981).

Not until recently was it recognized that the epidermis is an active participant in the body's immune system (Bergstresser, 1988). Several discoveries have led to this expanded view. First, the finding that dendritic LC express HLA-DR antigen, suggested that the epidermis contains antigen presenting cells (Katz, et al, 1982, Rowden, et al, 1977). Indeed, Sontheimer (1985) has shown that in the mixed epidermal cell lymphocyte reaction it is the LC which is responsible for activation of allogeneic lymphocyte proliferation (Sontheimer, 1985). Moreover, LC can present viral antigens (e.g., herpes simplex) as well as contact allergens (e.g., nickel sulphate) to sensitized lymphocytes (Braathen, et al, 1980; Braathen, 1980). After UV-irradiation, LC are less capable of alloantigen presentation than unirradiated LC and this decrease seems to be independent of a cytotoxic effect of UV light on LC (Cooper, et al, 1985). Secondly, the demonstration that epidermal cells produce factors, including epidermal cell thymocyte activating factor (ETAF), thymopoietin (Sauder, et al, 1982; Chu, et al, 1983) which affects lymphocyte function, and the documentation of T lymphocyte subsets with differential affinity for skin and its associated lymph nodes supported the notion that epidermal cells influence the circulating, "classical" immune competent cells (Streilein, 1983). Finally, the demonstration by ourselves and others that gamma interferon, a product of activated T cells, induces the synthesis and expression of HLA-DR antigen on benign and transformed keratinocytes further strengthened the concept that epidermal cells and immune competent cells interact in a reciprocal fashion (Basham, et al, 1984; Volc-Platzer, et al, 1985). All of these data would suggest that the skin plays an active role in the immune system.

A growing body of evidence suggests that emotion has an effect on susceptibility and resistance to disease (Golub, 1982). Several years ago it was shown in animal studies, for example, that hypothalamic lesions suppress the immune response (Cross, et al, 1980). At the cellular level, a number of intriguing correlations also have been discovered between the immune and neuroendocrine systems. For example, brain cells share an antigen with thymus-derived cells (Reif & Allen, 1964; Hamann, et al, 1980). Furthermore, it has been shown that upon stimulation lymphocytes produce alpha interferon, ACTH

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and endorphin-like substances (Smith & Blalock, 1981). Moreover, after stimulation with virus or bacteria, murine T lymphocytes produce enkephalin, a neurotransmitter with opiate-like activity (or at least its mRNA) (Zurawski, *et al*, 1986). ACTH, alpha-endorphin and enkephalins, in turn, can suppress murine lymphocyte function (Johnson, *et al*, 1982), whereas beta-endorphin potentiates T cell proliferative responses after the addition of the mitogens concanavalin A (con A) and phytohaemagglutinin (PHA) (Gilman, *et al*, 1982). Finally, corticosteroids, released in large amounts during periods of stress, are immunosuppressive and their metabolites may act directly on nerve cell membranes acting as an inhibitory or excitatory stimulus (Gilman, 1982; Majewska, *et al*, 1986). Thus, the neuroendocrine system may regulate the immune system and, by extension, the host resistance to infection.

OKT6 expressing cells which also demonstrate HLA-DR antigen but do not demonstrate Birbeck granules are found in the dermis and are termed indeterminate cells. These cells may represent LC precursor cells arriving via the dermis from the lymphatics or the peripheral circulation. Although normal individuals do not demonstrate OKT6 positive cells in their circulating blood, burn victims can show large numbers of these cells in the peripheral circulation (Wood, *et al*, 1984). How LC arrive in the skin remains obscure, but a recent report suggests that at least one regulating factor may be the expression of Ia antigen by epidermal keratinocytes (Roberts, *et al*, 1985). As indicated above, keratinocytes produce factors (ETAf/IL-1, thymopoietin) which have immunologic consequences. Moreover, incubation of keratinocytes with rIFN-gamma *in vitro* leads to a coordinated effect which I have termed the "gamma interferon effect" and which consists of induction of HLA-DR synthesis, ICAM like molecules and the stimulation and inhibition of certain proteins such as fibronectin and thrombospondin (Basham, *et al*, 1984; Nickoloff, *et al*, 1985, 1986, 1988, Morhenn, *et al*, 1985). Interestingly, Berman (1986) has shown that corticosteroids prevent the induction of HLA-DR antigen after rIFN-gamma treatment.

II. FINAL REPORT

1). Demonstration of mRNAs for IL-1 alpha and beta in keratinocytes. Keratinocytes secrete an IL-1 like substance (Sauder, 1982). In order to better characterize this IL-1 and to determine how its secretion is regulated, we studied the expression of the mRNA for this cytokine. The mRNA levels/cell presumably are constant, in contrast to the amount of protein/cell, which may be influenced by the amount of this protein present in the medium in which the cells are maintained. We have demonstrated mRNA for IL-1 alpha and beta in keratinocytes. These mRNAs are not expressed when the keratinocytes are cultured using serum containing medium, a condition under which the majority of the cells do not express the proliferative phenotype. By contrast, keratinocytes grown in keratinocyte growth medium (KGM), in which the vast majority of cells do express the proliferative phenotype, express mRNA for IL-1 alpha and a small amount of mRNA for IL-1 beta (see attached Abstract). Most recently, we have shown that when keratinocytes are grown in KGM but without the addition of cortisol, transforming growth factor alpha transforming growth factor alpha (TGF-alpha) induces keratinocytes to express mRNA for IL-6. This induction was not seen in KGM containing cortisol so that

the glucocorticosteroid presumably inhibits the expression of these mRNAs. This suggests that expression of mRNA levels for interleukin-1 alpha are regulated possibly by the state of differentiation of the keratinocyte. Furthermore, corticosteroids appear to have a regulatory effect on mRNA expression in these cells. This observation is extremely interesting in view of the profound (but poorly understood) clinical effect of glucocorticosteroids in a number of skin diseases.

In another set of experiments, we examined the effect of rIL-1 alpha on the levels of mRNA for TGF alpha and have shown a striking increase in expression of this mRNA resulting from the addition of this IL-1 to the culture medium (Morhenn, *et al*, 1989). Thus, it is conceivable that the previously described proliferative effect of IL-1 is actually an indirect effect of this cytokine mediated by an increase in synthesis of TGF-alpha, a known enhancer of keratinocyte proliferation (Pittelkow & Coffey, 1988). In this connection, recent demonstration that psoriatic epidermis contains significantly more mRNA for TGF-alpha as well as the protein itself is interesting (Elder, *et al*, 1989). Possibly, IL-1 produced by the activated lymphocytes in the dermis of psoriatic plaques causes the increase in TGF-alpha observed in these lesions and the hyperproliferation of keratinocytes found in this disease is secondary to this increase in TGF-alpha (not the IL-1 itself (see Section #3 below)). This would explain the clinical efficacy of drugs (e.g. methotrexate, cyclosporine A) which appear to primarily affect immune competent cells.

2). Characterization of the type of IL-1 present in human LC. LC maintained in serum containing medium express IL-1 beta mRNA but only after stimulation with phorbol myristate acetate (PMA) or LPS. Thus, the keratinocytes appear to make mainly IL-1 alpha whereas LC make mainly IL-1 beta which may reflect a possible regulatory pathway between the 2 cell types (see attached manuscript). Since PMA is not a "physiologic" substance in the body, we currently are testing other substances to see whether we can find a factor which is released by other skin cells which could activate LC.

3). The effect of recombinant interleukin-1 (rIL-1) alpha and beta on keratinocyte proliferation. We have confirmed our initial observation(s) that neither rIL-1 alpha or rIL-1 beta stimulate keratinocyte proliferation whereas these cells do express IL-1 receptors (see paper). By contrast, we were not able to confirm our preliminary results that recombinant interleukin-2 (rIL-2) stimulates keratinocyte growth. The rIL-2 has no effect on keratinocyte growth either alone or in combination with either of the above IL-1s. Our initial observation of stimulation was due to minute amounts of serum (less than 0.001%) present in the rIL-2 preparation initially used. These quantities of serum will of themselves stimulate keratinocyte proliferation in KDM (see attached paper). These observations are important because at least two published papers indicate that IL-1 stimulates keratinocyte growth *in vitro* (Gilcrest, *et al*, 1984; Ristow, 1987). Subsequently, a number of authors have suggested that the cause of the hyperproliferation of keratinocytes found in psoriasis is due to secretion of IL-1 by infiltrating, activated T cells (Nickoloff, 1988). Clearly, this hypothesis is not substantiated by our observations. The finding that rIL-2 does not stimulate keratinocyte proliferation *in vitro* is

interesting in view of the recent report that rIL-2 given to patients with malignancies (and a history of psoriasis) causes exacerbations of these patients' psoriatic disease process (Lee, et al, 1988). Thus, IL-2 must affect another cell type which in turn may secrete a cytokine which modifies keratinocyte proliferation.

4). In order to determine whether fibroblasts secrete a protein which affects keratinocyte growth, I entered into a collaboration with Drs. K. Neely and R. Rosenfeld. We have shown that normal keratinocytes and a human malignant cell line (SCL-1) express receptors for IGF-1/somatomedin-C as well as for IGF-2. For the SCL-1 cells we have demonstrated secretion of binding protein(s) for these two neuropeptides. Finally, IGF-1 stimulates ³H-thymidine incorporation into DNA in SCL-1 cells. Furthermore, preliminary experiments with normal keratinocytes indicate that IGF-1 causes a small stimulation of proliferation of these cells in keratinocyte defined medium (KDM).

5). Gamma-IFN induces the expression of several class II antigens. We have confirmed our initial observation that gamma-interferon causes the induction of both HLA-DP and -DQ antigens when keratinocytes are grown in KGM (see paper). That gamma-interferon induces class II antigens of the MHC other than HLA-DR is interesting in view of our previous finding that gamma-interferon treated keratinocytes are capable of inducing the proliferation of resting T cells (in the presence of rIL-2) but that this stimulation is not inhibited by a monoclonal antibody against HLA-DR antigen (Morhenn & Nickoloff, 1987).

6). The effect of macrophage colony stimulating factor-1 on LC and keratinocytes. We have not been able to stimulate the proliferation of either keratinocytes or LC with macrophage colony stimulating factor-1 (Cetus Corp.).

7). LC secrete tumor necrosis factor alpha. In collaboration with Drs. J. Larrick and T. Shi, I have confirmed the initial observation that LC contain tumor necrosis factor alpha (TNF-alpha). Furthermore, the LC contain the mRNA for this protein (see paper).

8). Effect of gamma-IFN on proteins secreted by keratinocytes. We have demonstrated that gamma-IFN treated keratinocytes reduce the synthesis of fibronectin and that this reduction of fibronectin in the culture medium is not simply due to increased proteolytic action of putative proteases induced by the gamma-interferon treated keratinocytes (see paper). This finding may be important for understanding the pathophysiologic mechanisms in wound healing.

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