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Invited Review Article

Clinical perspectives and murine models of lichenoid tissue reaction/interface dermatitis

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ABSTRACT

A set of histopathological elements, that is death of epidermal basal cell layer keratinocytes and inflammatory cell infiltration, distinguishes lichenoid tissue reaction (LTR)/interface dermatitis (IFD) from other inflammatory mucocutaneous diseases with histological findings of superficial perivascular dermatitis. The LTR/IFD is observed in inflammatory mucocutaneous diseases such as lichen planus, Stevens–Johnson syndrome/toxic epidermal necrolysis, acute graft-versus-host disease, lupus erythematosus and dermatomyositis. Clinical and basic researches have suggested that keratinocytes are antigen-presenting cells and mediate LTR/IFD reaction via production of cytokines/chemokines and inhibitory molecules such as programmed cell death (PD)-L1, and that cytotoxic $CD8^+$ T cells producing cytotoxic granules, perforin, granzyme B and granulysin are final effector cells to cause keratinocyte death. Because interferon-γ and FasL, which are produced by not only $CD8^+$ but also $CD4^+$ T cells, are candidates of the pathogenic molecules in LTR/IFD, $CD4^+$ T cells may also play a role to develop LTR/IFD. On the other hand, $CD4^+$ Treg cells accelerate the remission of LTR/IFD. Some murine models of LTR/IFD have been established. For example, LTR/IFD reactions were induced in keratinocyte-specific membrane-binding ovalbumin-transgenic (mOVA Tg) mice by adoptive transfer of $CD8^+$ T cells with OVA-specific T-cell-receptor. It has also been shown that human $CD8^+$ T cells are pathogenic immune cells in human skin-xenografted mice. Various immunosuppressants are used to treat patients with mucocutaneous diseases with LTR/IFD. By analysis of the mOVA Tg mice, a JAK inhibitor was suggested to be a new candidate drug to inhibit not only pathogenic T cells but also keratinocyte death in LTR/IFD. More specific treatments for patients with LTR/IFD will be developed in future.

Contents

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1. Introduction

A characteristic histopathological finding, death of epidermal basal keratinocytes and inflammatory cell infiltration, distinguishes lichenoid tissue reaction (LTR) from other inflammatory mucocutaneous diseases with superficial perivascular dermatitis. The pattern of epidermal basal keratinocyte injury by infiltrating inflammatory cells has been described as liquefaction/vacuolar degeneration. Because LTR is observed at the interface between the epidermis and the dermis, the majority of dermatologists and pathologists recently refer to LTR as interface dermatitis (IFD).

In 1973, Pinkus designated a number of inflammatory skin diseases with the characteristic histological pattern as LTR. LTR/IFD have been classified into "cell-rich" LTR/IFD with a high-density inflammatory infiltrate and "cell-poor" LTR/IFD with low-density infiltrate. Among autoimmune diseases, discoid lupus erythematosus (DLE) of patients with systemic/cutaneous LE (SLE/CLE) is included in a group of "cell-rich" LTR/IFD, while subacute CLE (SCLE) belongs to a group of "cell-poor" LTR/IFD as well as erythema of patients suffering from dermatomyositis (DM) and mixed connective tissue disease (MCTD). Lichen planus (LP; Fig. 1a), one of typical mucocutaneous diseases with LTR/IFD, displays "cell-rich" one as well as fixed drug eruption. Histological findings of "cell-poor" LTR/IFD are observed in eruptions of Stevens–Johnson syndrome (SJS)/toxic epidermal necrosis (TEN) and acute graft-versus-host disease (aGVHD; Fig. 1b). Therefore, LTR/IFD is a histological phenomenon observed in a number of severe and sometime fatal inflammatory mucocutaneous diseases.

It has been considered traditionally that apoptosis of keratinocytes at basal cell layer in LTR/IFD is mediated by $CD8^+$ T cells. In addition, other immune cells including $CD4^+$ T cells, dendritic cells (DCs) and Langerhans cells (LCs), and even target keratinocytes may play some roles in the reactions.

2. Keratinocytes

2.1. Keratinocyte death

Karatinocytes are target cells in LTR/IFD. Liquefaction/vacuolar degeneration in LTR/IFD by definition corresponds to rapid cytoplasmic swelling, which leads to rupture of the plasma membrane and organelle breakdown typically seen in necrosis of cells. Injury by cytokines, ribonucleotides, ATP depletion and ischemia can induce cellular necrosis as well as injury by toxins and oxidative stress. While histological findings suggest that epidermal basal keratinocytes are undergoing necrosis in LTR/IFD, apoptosis of keratinocytes has been detected by a TdT-mediated dUTP nick end labeling (TUNEL) assay or observations with an electron microscopy in skin lesions of aGVHD, CLE, and SJS/TEN [1–3]. Two major forms of cell death are identified, 'necrosis' characterized by organelle swelling and 'apoptosis' promoted by caspases. However, another form of programmed cell death independent of caspases has recently been identified, and termed necroptosis or programmed necrosis. Saito et al. observed keratinocytes with necrotic morphology, membrane breakdown and numerous swollen cellular organelles, as well as those with apoptosis morphology, a reduction of cellular volume and chromatin condensation, in specimens of erythematous lesions of SJS/TEN by electron microscopy [3]. It was also shown that a cytotoxic soluble factor, annexin A1, produced by peripheral blood mononuclear cells (PBMCs) from recovered SJS/TEN patients induced necroptosis of keratinocytes *in vitro* [3]. According to

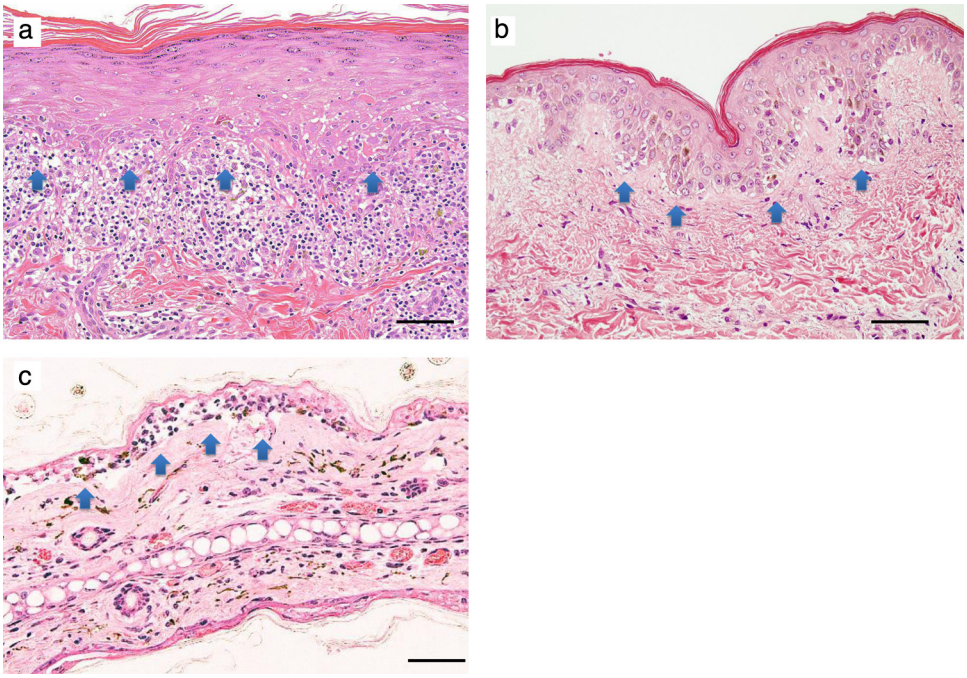

Fig. 1. Histological findings of LTR/IFD. (a) LP, (b) aGVHD, and (c) K14-mOVA Tg mice after transfer of OT-I cells.