Synopsis of Original Research Paper

Involvement of Macrophage Trafficking in Contact Dermatitis during Skin Sensitization

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During the sensitization phase of contact hypersensitivity through skin, it is widely accepted that Langerhans cells pick up antigens within epidermis and then migrate to the draining lymph nodes to present antigens to recirculating T lymphocytes in association with major histocompatibility complex class II molecules. We discovered trafficking of connective-tissue macrophages from dermis to draining lymph nodes during skin sensitization as an independent phenomenon from Langerhans cell trafficking using FITC as an antigen. We could differentiate trafficking of macrophages from that of Langerhans cells using monoclonal antibodies specific for macrophage calcium-type lectin (MMGL) that is a connective-tissue specific macrophage marker. The extent of dermal macrophage migration was greatly influenced by the selection of vehicles to dissolve FITC. Using several kinds of vehicles, we observed a positive correlation between the efficiency of skin sensitization and the extent of macrophage migration. These results indicated that chemicals in the vehicles may exhibit an adjuvant activity through the induction of tissue macrophage trafficking. We directly demonstrated macrophages migration upon skin sensitization by local cell transfer experiments. Interestingly, the migration was induced by vehicle alone, such as acetone/dibutyl phthalate (AD), without FITC. These results also confirmed the critical role of vehicles with adjuvant activity.

We observed the initiation of dermal macrophage trafficking using mouse skin after epicutaneous application of AD. Thus, we immunohistochemically detected that MMGL-positive dermal macrophage density was transiently and reversibly decreased after epicutaneous application of AD. We also developed an organ culture system, in which skin fragments taken from the site of AD application were subjected to a short term organ culture. The density of MMGL-positive dermal macrophage decreased irreversibly in this system. Using the organ culture system, we discovered that AD treatment induced local production of pro-inflammatory cytokines during skin sensitization. Furthermore, we also found the activity that induces dermal macrophage exit was mediated by pro-inflammatory cytokines, such as IL-1β, using recombinant cytokines and antibodies against cytokines. A possibility that IL-1β treatment down regulates MMGL expression in macrophages has been excluded.

In conclusion, our studies revealed importance of connective tissue macrophage trafficking during skin sensitization as a mechanism of adjuvant activity of chemicals. Our ex vivo organ culture system using skin fragments will be useful to examine chemicals that might enhance skin sensitization.