—Photogravure—

Requirement of E-cadherin Interactions for Langerhans Cell Differentiation

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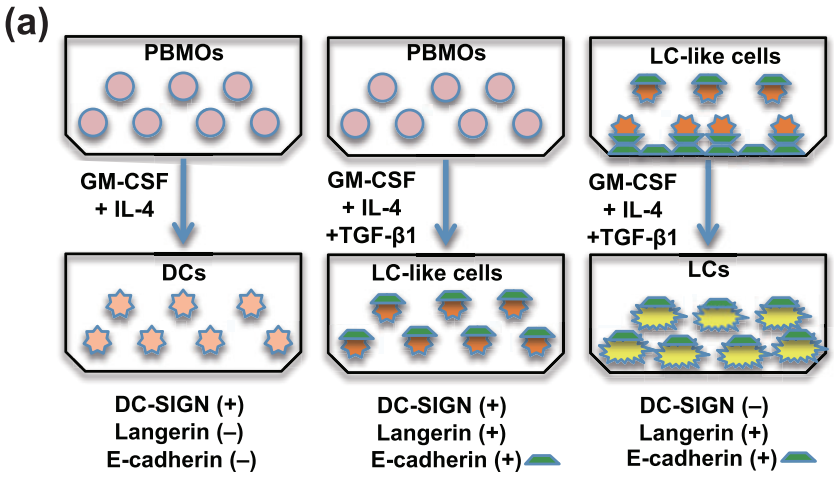

Fig. 1–1

Skin and mucosal tissues contain 2 distinct subsets of dendritic cells (DCs). One subset comprises Langerhans cells (LCs) expressing langerin but not DC-specific intracellular adhesion molecule 3-grabbing nonintegrin (DC-SIGN) localized in the epidermis. The other subset comprises DCs expressing DC-SIGN but not langerin observed in the mucosal subepithelial layer and dermis of the skin. Peripheral blood monocytes (PBMOs) might differentiate into DCs when co-cultured in the presence of interleukin (IL) 4 and granulocyte-macrophage colony-stimulating factor (GM-CSF) **(left panels of Fig. 1(a))** or into LC-like cells in presence of IL-4, GM-CSF, and transforming growth factor (TGF) β1 **(middle panels of Fig. 1(a))**[1]. However, these LC-like cells expressed DC-SIGN and E-cadherin as well as langerin. When these E-cadherin-positive LC-like cells were co-cultured with keratinocytes also expressing E-cadherin, expression of DC-SIGN on these LC-like cells was strongly down-modulated, and their phenotype became similar to that of purified epidermal LCs. Moreover, the LC-like cells became LCs when incubated on E-cadherin-coated plates **(right panels of Fig. 1(a))**, indicating E-cadherin-E-cadherin interactions are required for monocytes to differentiate into langerin-positive, DC-SIGN-negative, monocyte-derived LCs (moLCs)[2].

The phenotypic features of these moLCs closely resembled those of skin-derived epidermal LCs (primary LCs), in that they expressed the LC-specific markers CD1a and langerin and contained Birbeck granules, as determined with electron microscopic analysis **(Fig. 1(b))**. In our previous study, we showed that purified primary LCs from human skin does not express Toll-like receptor (TLR) 4 and expresses little or no TLR[3]. Similar to primary LCs, moLCs did not express TLR4 and had a low expression of TLR2 and TLR3 at the messenger RNA level **(Fig. 1(c))**. Therefore, moLCs induced through E-cadherin-E-cadherin interactions show a great phenotypic resemblance to epidermal LCs.

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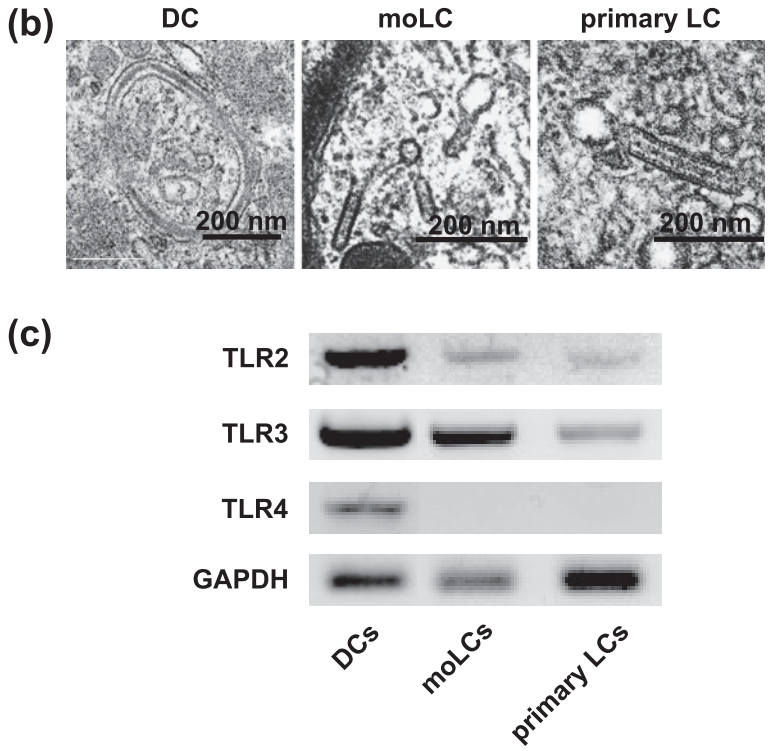

Fig. 1–2

Fig. 1 (a) When CD14-positive PMBOs were cultured for 6 days in the presence of 100 ng/mL GM-CSF and 10 ng/mL IL-4, DC-SIGN-positive but not langerin-negative DCs were obtained (a: left panels). However, when cultured for 6 days with 100 ng/mL GM-CSF, 10 ng/mL IL-4, and 10 ng/mL TGF-β1, LC-like cells expressing DC-SIGN and E-cadherin as well as langerin were induced (a: middle panels). When PBMO-derived E-cadherin-positive LC-like cells cultured for 3 days were incubated on E-cadherin-coated plates for an additional 3 days, E-cadherin-positive, langerin-positive, DC-SIGN-negative moLCs were induced (a-middle panels). (b) Birbeck granules were identified with electron microscope analysis within moLCs and skin-derived primary LCs. (c) The expression of TLRs within PBMO-derived DCs, moLCs, and primary LCs was analyzed with reverse transcriptase-polymerase chain reaction analysis.

References

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