Tissue-resident memory T (Trm) cells form a heterogeneous population that provides localized protection against pathogens. Here, we identify CD49a as a marker that differentiates CD8+ Trm cells on a compartmental and functional basis. In human skin epithelia, CD8+CD49a+ Trm cells produced interferon-γ, whereas CD8+CD49a− Trm cells produced interleukin-17 (IL-17). In addition, CD8+CD49a+ Trm cells from healthy skin rapidly induced the expression of the effector molecules perforin and granzyme B when stimulated with IL-15, thereby promoting a strong cytotoxic response. In skin from patients with vitiligo, where melanocytes are eradicated locally, CD8+CD49a+ Trm cells that constitutively expressed perforin and granzyme B accumulated both in the epidermis and dermis. Conversely, CD8+CD49a− Trm cells from psoriasis lesions predominantly generated IL-17 responses that promote local inflammation in this skin disease. Overall, CD49a expression delineates CD8+ Trm cell specialization in human epithelial barriers and correlates with the effector cell balance found in distinct inflammatory skin diseases.