The Skin Is a Site of Long-Term Viral Persistence Associated with Retention of Antiviral Memory T Cells

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In this issue of *Dermatology*, Bonvicini et al. [1] demonstrate that human parvovirus B19 (B19) DNA can be detected not only in pityriasis lichenoides lesions, but also in healthy control skin without clinical symptoms at equivalent frequencies [2]. More importantly, they show that B19 DNA can be detected more frequently in skin samples from young individuals (≤ 20 years old) than in those from older ones. These findings indicate that B19 DNA can be universally detected in the skin following primary infection, particularly in young immunocompetent individuals, regardless of whether they have symptoms, and suggest that human skin cells may be persistently infected with B19 for a long period after primary infection despite the appearance of specific IgG antibodies. Indeed, according to their findings, B19 persistence would last < 20 years after the initial infection in the half of healthy individuals. The study by Bonvicini et al. [1] is impressive, but some crucial issues warrant further investigation: the possibility that fragments of DNA instead of full virions from a past infection persist in the skin remains to be determined. In addition, it is also unknown whether or not productive replication of this virus occurs even in healthy control skin. However, normal-appearing skin is likely to harbor a variety of functional viral ge-

nomes, but fail to produce virions; thus, different viruses may establish a latent infection in the skin and the asymptomatic recurrence would occur. Similar findings have been also reported in rheumatoid arthritis: B19 DNA is present in the inflamed joints, but is also detected in an equivalent proportion of control samples of synovial tissues [3]: these findings do not support the potential contribution of B19 in the pathogenesis of rheumatoid arthritis. Nevertheless, the finding reported by Bonvicini et al. [1] is somewhat surprising in view of the previous belief that many viruses such as B19 are fully eradicated from the host by the combined effect of the cellular and humoral immune responses generated following the primary infection. It is now clear that the previous belief needs to be reassessed.

B19 infects erythroid-lineage cells through P antigen and causes various clinical symptoms, such as erythema infectiosum [2, 4] gloves and socks syndrome [5], Henoch-Schönlein purpura [6], arthropathy, or transient aplastic crisis [4] in humans. In addition to blood group P antigens, $\alpha_5\beta_1$ integrin [7] and Ku80 autoantigen [8] have been reported to be the cellular coreceptors for B19 infection. The results of experimental inoculation of normal volunteers with this virus demonstrated that fever

and nonspecific influenza-like symptoms occur early in the course of acute infection while cutaneous eruptions and rheumatic symptoms develop later, about 2 weeks after the initial infection, coincident with the appearance of antiviral antibodies [4]; thus, these symptoms are likely due to the formation and deposition of immune complexes in the skin and joints. Although the presence of B19 DNA in the lesions was taken as proof of the cause of the disease in most previous studies [9], it has become obvious that we cannot accept B19 as the causative agent of a given disease simply because of the mere presence. Indeed, the study by Bonvicini et al. [1] clearly indicates that the detection of B19 DNA in lesional skin by a PCR technique cannot be used as proof of the cause of the disease. How then can an etiological role of B19 be proven in a given disease? In this regard, it is important to demonstrate localization of the virus DNA or RNA in situ within the lesional skin. Indeed, although this virus exhibits a special tropism for the human erythroid progenitor, B19 transcripts, B19 protein and viral protein 1 have been shown to be present in T cells, B cells, macrophages, and follicular dendritic cells [8]. B19 RNA has also been demonstrated to be localized in situ to the cutaneous and glomerular capillary endothelium by using reverse transcriptase in situ PCR techniques [6]. We therefore have to await the result of in situ PCR studies on the direct localization of the viral DNA or RNA to various types of cells infiltrating or resident within the evolving skin lesions and healthy control skin, before discarding the possibility of an etiological role of B19 in the pathogenesis of a given disease.

While the skin contains many specialized cell types that can serve as targets for specific viruses, the skin is also a hostile environment for other viruses. Due to their specific location in the dermis and subepithelium, dendritic cells (DCs) serve to capture various invading pathogens such as HIV, human cytomegalovirus, measles virus and human herpes virus (HSV) and are able to transmit these viruses to target cells through the DC-specific C-type lectin DC-SIGN [10, 11]. Interestingly, HSV-infected DCs have been shown to become resistant to further maturation stimuli supplied by LPS, TNF- α or CD40L [12], through downregulation of the key costimulatory molecules such as CD40, CD80, CD83, and CD86. Such virus-mediated downregulation of costimulatory molecules and virus-induced apoptosis would favor viral spread and persistence, although the immunoevasive mechanisms used by HSV and probably other viruses residing in the skin could be counteracted by cross-presentation of the HSV antigen contained within these apoptotic cells by

uninfected bystander DCs. Varicella-zoster virus can also be transferred from DCs to infect CD4 and CD8 T cells. Mast cells located in the perivascular area are also an important member of cellular reservoirs for HIV and other viruses. Although it is generally believed that such persistence of herpesviruses and other viruses in the skin is detrimental to the host, recent studies have suggested an alternative view that HSV persistence in the skin confers a surprising benefit to the host by upregulating the basal activation state of local innate immunity against subsequent bacterial infections [13]. Because the skin is composed of heterogeneous types of susceptible cells considered as potential sanctuaries of persistent infections, such as DCs, mast cells and endothelial cells, viral persistence in these cells resident in the skin might provide a means of protecting the host from more dangerous invading pathogens.

We previously demonstrated that a significant number of CD8⁺ T cells with the effector-memory phenotype reside along the epidermal basal layer in fixed drug eruption lesions and even in normal-appearing skin, although much less in the latter, and consistently express an activation marker CD69 [14] despite no antigenic stimuli. This finding, when combined with fact that functional T cell memory requires a persistent antigen, suggests that virus-specific CD8⁺ T cells are selectively retained in an activated memory phenotype in the skin due to persistent low-level antigenic stimulation provided by latent viruses such as HSV and B19.

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