we set forth to identify viral genome in the endothelium of the vasculitic lesions. Cell-mediated immune (CMI) dysfunction, including defective natural killer cell function has been documented in patients with XLP, and defective CMI may result in altered EBV tissue tropism as we suggest. We agree that many more patients, as well as controls, would need to be studied to definitively answer this issue. The functionality of EBV-specific CTL remains a subject for debate.\(^1,^9\) Normal EBV-specific CTL function, as has been detected in some patients with XLP, might indeed explain the targeted assault and damage of the infected vascular structures that we have demonstrated.

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References


To the editor:

Langerhans cells and the cells of Langerhans cell histiocytosis do not express DC-SIGN

Geissmann and colleagues recently reported that cells of Langerhans cell histiocytosis (LCH) in osseous and/or chronic lesions have an immature dendritic cell phenotype.\(^1\) In addition to CD1a, LCH cells in all 25 cases examined expressed Langerin, a recently described C-type lectin that appears to be restricted entirely to Langerhans cells.\(^2\)

An increasing number of dendritic cell subsets, such as dendritic cell–specific ICAM-grabbing nonintegrin (DC-SIGN), dendritic cell immunoreceptor (DCIR), DEC-205, and CD23, are now recognized.\(^3\) We consider it important to determine whether these lectins are expressed on similar, overlapping, or mutually exclusive dendritic cell subsets, as such information may suggest the biological roles of the individual lectins. Our recent work has focused on DC-SIGN (manuscript submitted and Soilleux et al\(^4\)), which has 32% sequence identity at the amino acid level to Langerin across the carbohydrate recognition domain. DC-SIGN has the capacity to bind the HIV surface molecule glycoprotein 120 in an inhibitable manner by mannose,\(^5,^6\) as well as the lymphocytic surface-expressed molecule ICAM-3,\(^7\) and the endothelial surface molecule ICAM-2.\(^8\) Langerin also possesses the critical mannose binding motif seen in DC-SIGN. It has not yet been determined whether HIV may interact with Langerin in a manner analogous to its interaction with DC-SIGN.

We have recently demonstrated that DC-SIGN is expressed by cells with an immature dendritic cell phenotype (manuscript submitted) similar to that described by Geissmann et al\(^1\) in LCH cells. In our study, the DC-SIGN\(^+\) cells were CD14\(^-\) low HLA-DR\(^+\)low CD68\(^-\) 8100\(^+\) and only rarely expressed dendritic cell activation markers such as CD83, CD86, and cmrf-44 (manuscript submitted). Moreover, the DC-SIGN\(^+\) cells were consistently negative for CD1a (manuscript submitted). Cells matured in the presence of granulocyte-macrophage colony-stimulating factor (GM-CSF), tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)), transforming growth factor \(\beta\) (TGF-\(\beta\)), stem cell factor (SCF), and flt-3 ligand from CD34\(^+\) lin\(^-\) peripheral blood cell precursors, to give a Langerhans cell phenotype,\(^9\) showed no evidence of DC-SIGN expression by reverse transcriptase–polymerase chain reaction (RT-PCR).\(^8\) Dendritic cells matured from peripheral blood monocytes in the presence of GM-CSF and interleukin-4 (IL-4) and could be shown to express matured from peripheral blood monocytes in the presence of GM-CSF and interleukin-4 (IL-4) and could be shown to express DC-SIGN–expressing cells could be seen in surrounding tissue acting as a useful internal positive control (Figure 1C-D). Our data in accordance with previous results suggesting that expression of DC-SIGN and expression of the Langerhans cell–restricted molecule CD1a are mutually exclusive (manuscript submitted, Soilleux et al\(^4\) and Geijtenbeek et al\(^4\)). Our findings, when considered with those of Geissmann et al, indicate that DC-SIGN is only expressed on a subset of dendritic cells with an immature phenotype. Given the very similar expression patterns of Langerin and CD1a,\(^4\) our data suggest that DC-SIGN and Langerin are expressed by mutually exclusive dendritic cell subsets. Whether there are functional differences between Langerhans cells and DC-SIGN\(^+\) dendritic cells remains to be determined. The 2 novel
C-type lectins, Langerin and DC-SIGN, may have analogous properties on separate dendritic cell subsets with respect to, for example, their capacity to bind T lymphocytes and lentiviruses.

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References


To the editor:

Phenotype and genotype expression in pseudohomozygous R2 factor V

Factor Va is the important cofactor for prothrombinase. Factor Va is inactivated by activated protein C (APC) following 3 cleavages of the heavy chain at Arg306, Arg506, and Arg679.1 Cleavage of normal factor Va by APC at these sites results in the production of Mθ 45 000, Mθ 30 000, Mθ 22 000 and 20 000 fragments. In plasma, following the addition of APC and a synthetic membrane surface (phosphatidylcholine phosphatidylserine [PCPS]), appearance of the Mθ 30 000 fragment demonstrates cleavage of normal factor V at Arg306 and Arg506.2 The Mθ 30 000 fragment can be detected in plasma by using an anti–human factor V monoclonal antibody that recognizes an epitope located between residues 307 and 506 of the molecule.2,3

The R2 haplotype in factor V is characterized by an A4070G substitution (His1299Arg) in the factor V molecule and is associated with mild APC resistance, but the underlying molecular mechanism remains unclear. We have recently described a thrombotic family with 4 symptomatic members.2 One of them (I3) was doubly heterozygous for the factor V HR2 haplotype and for the factor V Tyr1702Cys mutation, causing CRM–factor V deficiency. Since the factor V allele predicting the Tyr1702Cys substitution is not expressed at the protein level,3 the plasma of this patient contains only R2 factor V, in accordance with her reduced factor V levels (FV:Ag 43%; FV:C 36%; normal range 70%-130%) and mild APC resistance (nAPC-sr 0.72, normal values > 0.84). We have concluded that while the His1299Arg substitution in factor V induces APC resistance, the presence of the Tyr1702Cys mutation was responsible for absence of expression of the corresponding allele (previously reported to result in CRM–factor V deficiency). This particular condition (pseudohomozygosity for the factor V HR2 haplotype) offers the opportunity to study the APC-mediated inactivation of R2 factor Va in plasma, which is otherwise possible only in the rare (~0.4% of the general population) homozygous individuals.

Molecular investigations were undertaken in this thrombotic patient (I3, see Castoldi et al). The patient was found to be heterozygous, at both the DNA and messenger RNA (mRNA) levels, for the His1299Arg and Asp2194Gly substitutions, characterizing the HR2 haplotype as well as for the Tyr1702Cys mutation in factor V. No mutation, in addition to the polymorphic
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