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and found that patients with priapism were more likely to be homozygous for hemoglobin S (HbSS) disease (less likely to have HbSC [compound heterozygosity for HbS and HbC] disease and HbSS-α thalassemia) and to have elevated markers of hemolysis and inflammation. Multivariate analysis identified lactate dehydrogenase, reticulocyte count, and platelet count as independently associated with priapism. The authors conclude that priapism, pulmonary hypertension, and possibly ischemic stroke are all associated with low steady-state hemoglobin levels, protection by α thalassemia, and HbSC disease, and may be considered a subphenotype of sickle cell disease mechanistically linked to hemolytic anemia, reduced NO bioavailability, and vasculopathy.

In conclusion, biochemical, physiologic, and epidemiologic data suggest that chronic intravascular hemolytic anemia, while silent from a vaso-occlusive pain crisis standpoint, leads to sustained NO depletion, oxidant stress, vasoconstriction, and proliferative vasculopathy in a number of organ systems, ultimately contributing to the development of priapism, cutaneous leg ulceration, pulmonary hypertension, sudden death, and possibly stroke (Figure). The existence of such a subphenotype suggests new directions for therapy (targeting hemolytic anemia with higher levels and pancellular penetrance of hemoglobin F, inhibiting the Gardos channel to limit hemolysis, increasing NO bioavailability, and reducing superoxide formation) and combination therapy, with transfusions and hydroxyurea aimed at inhibiting erythropoiesis. ■

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IMMUNOBIOLOGY

Comment on Tan et al, page 2936

Costimulatory blockade: act II

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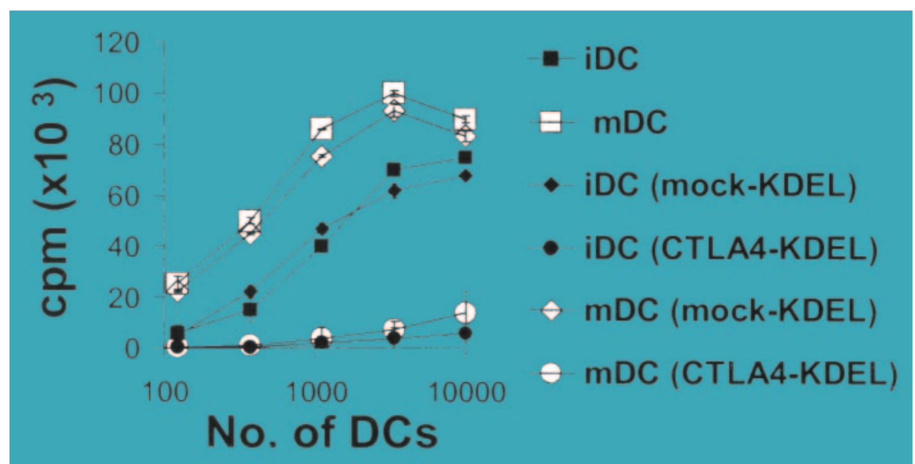
Dendritic cells with low expression of B7 molecules tend to induce tolerance, but it has been difficult to show that the observations are related. A new study suggests that they may be.

Recently, it has become clear that "resting" (unactivated or immature) dendritic cells (DCs) can induce immunologic tolerance in responding T cells.[1] This pathway may be important in maintaining tolerance toward antigens in the periphery. However, it has been less clear exactly why resting DCs are tolerogenic.[2] One leading hypothesis (reviewed in Redmond and Sherman[3]) has focused on the fact that these DCs express low levels of the costimulatory molecules B7-1/CD80 and B7-2/CD86. Since costimulation is important for successful T-cell activation, it has been proposed that the lack of B7-1/B7-2 is the direct, mechanistic cause of anergy and tolerance induced by resting/immature DCs. However, there has been relatively little firm experimental evidence available to directly support this hypothesis.[2]

Attempts to answer the question using B7-1/B7-2 knock-out mice have been somewhat ambiguous, due to the multiple developmental immunologic defects (including abnormalities in both immunity and tolerance) present in these mice. A second strategy has attempted to mask or block B7 molecules using a soluble fusion protein incorporating the high-affinity B7-binding site of the cytotoxic T lymphocyte antigen 4 (CTLA4) molecule. Experimentally, this CTLA4-immunoglobulin construct (CTLA4-Ig) can indeed induce immunosuppression and tolerance in certain settings, although the results have been variable. Interpretation has been further complicated by the fact that CTLA4-Ig can also induce the immunosuppressive enzyme indoleamine 2,3-dioxygenase (IDO).[4]



Transfection of DCs with CTLA4-KDEL. See the complete figure in the article beginning on page 2936.

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To help clarify this rather complex situation, Tan and colleagues now bring the novel strategy of binding and destroying the B7 molecules in DCs before they have a chance to reach the cell surface. The authors used the B7-binding portion of CTLA4 but modified it to include a retention signal that targets it to the endoplasmic reticulum. When this construct was transfected into human monocyte-derived DCs, it markedly reduced the cell-surface expression of B7-1 and B7-2, and—just as theory would predict—rendered the DCs tolerogenic in vitro. This was accomplished without inducing IDO in the DCs (unlike CTLA4-Ig) and apparently also without inducing other changes to the basic DC biology (at least not obvious ones).

Thus, this study offers novel support for the hypothesis that it is simply the absence of B7 expression that renders the DCs tolerogenic. This interpretation of the authors' data remains still somewhat speculative and will need to be more directly tested in the future (eg, by artificially ligating the appropriate costimulatory counter-receptor on the T cells to test whether this bypasses the tolerogenic effects of the transfected DCs). It will also be important to definitively rule out that the formation and degradation of intracellular CTLA4/B7 complexes do not somehow alter the basic biology of the DCs. But these questions notwithstanding, from a therapeutic standpoint the results of Tan and colleagues suggest a novel and intriguing strategy that might render human monocyte-derived DCs stably tolerogenic in vivo. ■

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● ● ● PHAGOCYTES

Comment on Cao et al, page 3234

Mac-1 mediates migration to lymph nodes

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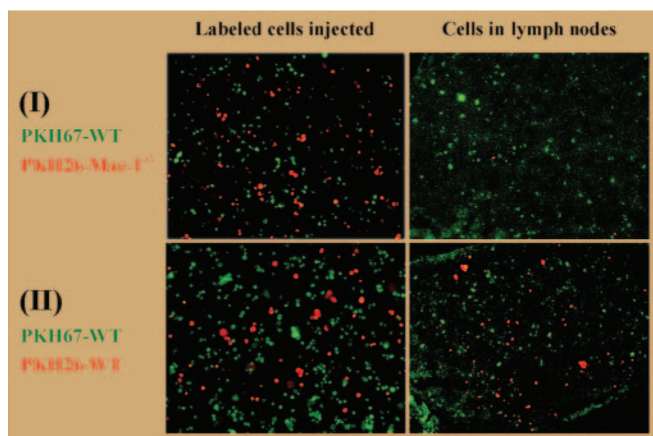
Bacterial lipopolysaccharide induces macrophages to migrate from inflamed tissues to lymph nodes using the adhesion molecule Mac-1.

Cell migration requires attachments to cells and matrix by adhesion molecules. Mac-1, also known as CD11b/CD18, $\alpha_M\beta_2$ integrin, or complement receptor 3, is an adhesion molecule expressed by a variety of phagocytes including macrophages in inflammatory sites. In the present issue, Cao and colleagues demonstrate that Mac-1 mediates a bacterial lipopolysaccharide (LPS)–induced migration of macrophages out of inflamed tissues and into the lymph nodes.



Macrophage migration from the peritoneum to the lymph nodes. See the complete figure in the article beginning on page 3234.

Proinflammatory stimuli including LPS can render macrophages difficult to extract from body cavities using lavage. In the present studies, Cao and colleagues observed that LPS decreased the numbers of macrophages that could be lavaged from thioglycollate-inflamed wild-type (WT) mice, but LPS did not affect the numbers of thioglycollate-elicited macrophages lavaged from Mac-1–deficient mice. Therefore, Mac-1 is necessary to whatever makes thioglycollate-elicited macrophages refractory to lavage after LPS stimulation.

To determine how LPS affected such macrophages, Cao and colleagues transferred fluorescent thioglycollate-elicited macrophages to thioglycollate-inflamed peritoneal spaces and tracked them after injecting saline or LPS. LPS but not saline induced the fluorescent macrophages to adhere to peritoneal surfaces within 5 minutes. However, by lavage time (4 hours after LPS injection), these cells were no longer present in either the peritoneal lavage fluid or on the peritoneal surfaces; instead, they were in the draining lymph nodes and the circulating blood. When Mac-1 was inhibited in these WT mice by a soluble antagonist of Mac-1 (neutrophil inhibitory factor), more macrophages could be recovered by lavage and fewer macrophages appeared in the lymph nodes. When fluorescent Mac-1–deficient macrophages were injected into Mac-1–deficient hosts, LPS failed to induce the adhesion of fluorescent cells to the peritoneal surfaces and fluorescent cells did not appear in the lymph nodes or blood. Labeling thioglycollate-elicited WT macrophages green and thioglycollate-elicited Mac-1–deficient macrophages red allowed these different cells to be mixed together and then studied within the same WT mice with thioglycollate-induced peritonitis. After LPS injection, red Mac-1–deficient macrophages but not green WT macrophages were recovered by lavage, whereas green WT but not red Mac-1–deficient macrophages appeared in the lymph nodes (see figure). Altogether, these data make a compelling argument for Mac-1–mediated migration of macrophages to the lymph nodes in this inflammatory setting.

Mechanisms by which macrophages migrate to the lymph nodes are beginning to be elucidated.[1] LPS must induce changes in chemokines, adhesion molecules, and other factors to mediate this transit of inflammatory macrophages. The initial tight adhesion to peritoneal surfaces mediated by Mac-1 may be critical to the ensuing migration. This initial adhesion occurs within 5 minutes after LPS injection, suggesting that it does not require new gene expression. The Mac-1 ligands essential for attachment to peritoneal surfaces and migration to the lymph

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