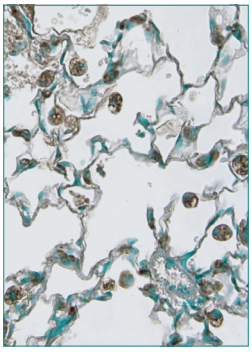
JCI The Journal of Clinical Investigation

In This Issue

J Clin Invest. 2006;116(3):551-551. https://doi.org/10.1172/JCI120031.

In this issue

Elastin breakdown builds up inflammation in emphysema Pulmonary emphysema is an obstructive lung disease that primarily affects smokers. Smoke-induced enzymes called proteases are hypothesized to cause emphysema directly through degradation of lung parenchymal collagen and elastin. Now, Houghton et al. show that elastin fragments (EFs) resulting from the degradation of elastin by elastases such as the macrophage metalloelastase MMP-12 potentiate inflammation and emphysema in mice (pages 753–759). In the current study, the authors report that bronchoalveolar lavage fluid (BALF) and lung homogenates from smoke-exposed wild-type mice contain significant monocyte chemotactic activity compared with samples from smoke-exposed MMP-12–/– mice, even though levels of chemokines such as MCP-1 and MIP-1α were similar in both groups. Importantly, this difference was not attributed merely to the presence of MMP-12, as MMP-12 itself is not chemotactic. Western blotting of BALF identified 45-kDa EFs in the chemotactic fractions. To directly demonstrate the chemotactic ability of EFs, the authors treated smoke-exposed or pancreatic elastase–treated mice with an antibody against EFs, which reduced macrophage accumulation in the lung and airspace enlargement. Together, the results of this study suggest that degradation products of elastases perpetuate inflammation and further proteolysis in this and potentially other protease-associated diseases. Rejection hurts: activated platelets in organ transplantation Organ transplantation, by necessity, involves surgically induced physical trauma at the time the tissue graft is […]



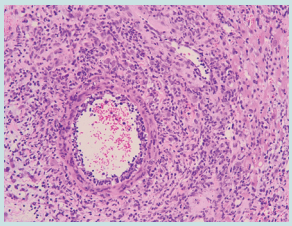
Elastin breakdown builds up inflammation in emphysema

Pulmonary emphysema is an obstructive lung disease that primarily affects smokers. Smoke-induced enzymes called proteases are hypothesized to cause emphysema directly through degradation of lung parenchymal collagen and elastin. Now, Houghton et al. show that elastin fragments (EFs) resulting from the degradation of elastin by elastases such as the macrophage metalloelastase MMP-12 potentiate inflammation and emphysema in mice (pages 753–759). In the current study, the authors report that bronchoalveolar lavage fluid (BALF) and lung homogenates from smoke-exposed wild-type mice contain significant monocyte chemotactic activity compared with samples from smoke-exposed MMP-12$^{-/-}$ mice, even though levels of chemokines such as MCP-1 and MIP-1α were similar in both groups. Importantly, this difference was not attributed merely to the presence of MMP-12, as MMP-12 itself is not chemotactic. Western blotting of BALF identified 45-kDa EFs in the chemotactic fractions. To directly demonstrate the chemotactic ability of EFs, the authors treated smoke-exposed or pancreatic elastase–treated mice with an antibody against EFs, which reduced macrophage accumulation in the lung and airspace enlargement. Together, the results of this study suggest that degradation products of elastases perpetuate inflammation and further proteolysis in this and potentially other protease-associated diseases.

Reversal of misfortune in Alzheimer disease

The destruction of cholinergic neurons in the hippocampus in Alzheimer disease (AD) has led researchers to investigate cholinergic dysfunction as a primary cause of AD. Evidence also suggests that amyloid β (Aβ) peptide deposits contribute to AD-associated memory deficits. In this issue, Bales and colleagues integrate these 2 mechanisms by showing reduced hippocampal acetylcholine (ACh) release in transgenic mice overexpressing human Aβ, known as PDAPP mice (pages 825–832). Although levels of the ACh precursor choline were elevated in PDAPP mice compared with wild-type mice, mRNA levels of the neuronal high-affinity choline transporter ChT-1 were similar, suggesting that Aβ did not affect ACh biosynthesis. To identify the cause of the choline elevations, the authors performed coimmunoprecipitation studies of hippocampal homogenates and identified a direct interaction between Aβ peptide and ChT-1 in PDAPP animals. Disruption of this interaction using an anti-Aβ antibody not only restored hippocampal ACh release, but also improved a measure of learning called habituation in the PDAPP mice. Taken together, these data demonstrate that disruption of the direct interaction between Aβ and ChT-1 using an anti-Aβ antibody may be an effective approach to improving memory and cholinergic dysfunction in AD through the restoration of ACh release.

Rejection hurts: activated platelets in organ transplantation



Organ transplantation, by necessity, involves surgically induced physical trauma at the time the tissue graft is encountered by the immune system. CD154 is a surface protein found on activated T cells, and its blockade has been shown to prevent graft rejection. However, CD154 is also released in soluble form by activated platelets. To date, there has been no direct evidence that this form of the molecule independently mediates any pathological immune response. Xu and colleagues now show that CD154 released from surgically activated platelets is sufficient to induce cardiac allograft rejection independently of cell-bound CD154 (pages 769–774). The authors studied CD154-knockout mice with cardiac allografts and found that, although normally these mice are resistant to graft rejection, the animals demonstrated acute cellular rejection following treatment with CD154-expressing human platelets or soluble CD154. To identify the specific role of CD154 in this process, the authors treated the mice with a human CD154–specific antibody (5c8), which prevented the induced rejection. The data in this study demonstrate that, in addition to the previously established role of T cell–expressed CD154 in immune responses, the soluble form of this protein released by activated platelets mediates rejection, providing a link between trauma and acquired immune system activation.

Pericytes help limit tumor metastasis

The spreading of tumor cells from a primary tumor to a distant site via the blood involves changes in cell-cell adhesion, cell-ECM adhesion, cell motility, and epithelial-mesenchymal conversion of tumor cells, but the underlying cause for the escape of these cells into the vasculature is largely unknown. One potential mechanism is suggested by the increased metastases observed in mice deficient in neural cell adhesion molecule (NCAM). Now, Xian and colleagues report that pancreatic tumors in NCAM-deficient mice spread to other organs because pericytes are unable to interact properly with endothelial cells in the vessel wall (pages 642–651). The authors found that the tumors in NCAM-deficient mice sprouted leaky blood vessels that allowed tumor cells to metastasize. In addition, mice genetically modified to be deficient in the pericyte recruitment protein PDGF demonstrated metastases to the liver, kidney, and intestines, suggesting that loss of specific interactions between endothelial cells and pericytes are important in tumor cell spread. The authors suggest that NCAM limits tumor cell metastasis through its promotion of pericyte interactions, thus identifying a new mechanism for tumor cell migration.