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In This Issue

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PPARγ ligands and monocyte recruitment (See article on pages 793–802.) Oxidized LDL (oxLDL), generally accepted as the major source of cholesterol during foam cell formation in the developing atherosclerotic plaque, exerts a number of other biological effects that could also contribute to coronary artery disease. For example, oxLDL is directly cytotoxic, and it profoundly affects endothelial cell adhesion and the secretion of monocyte chemoattractant protein-1 (MCP-1). Here, Han et al. explore another potentially atherogenic function of oxLDL, its ability to suppress transcription of CCR2, a monocyte receptor for MCP-1. Once monocytes have migrated to the arterial intima, an environment that can be rich in oxLDL, the loss of CCR2 may favor their accumulation. Because this environment promotes their differentiation to macrophages and, later, to lipid-laden foam cells, the recruitment of monocytes is thought to contribute to vessel pathology. The authors show that monocytes interact with oxLDL primarily through the scavenger receptor CD36, and they argue that uptake of oxidized lipid from the oxLDL particle is required for CCR2 downregulation. Since this effect can be mimicked by providing cells with pure oxidized fatty acids that are ligands for the transcription factor PPARγ, Han et al. tested the effects on CCR2 expression of another known PPARγ agonist, the antidiabetic drug BRL49653 (rosiglitazone). A recent JCI paper from some of the same authors […]

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By John Ashkenas, Science Editor

PPARγ ligands and monocyte recruitment

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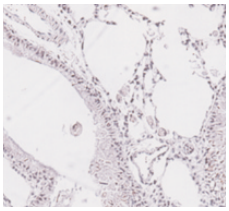
Oxidized LDL (oxLDL), generally accepted as the major source of cholesterol during foam cell formation in the developing atherosclerotic plaque, exerts a number of other biological effects that could also contribute to coronary artery disease. For example, oxLDL is directly cytotoxic, and it profoundly affects endothelial cell adhesion and the secretion of monocyte chemoattractant protein-1 (MCP-1). Here, Han et al. explore another potentially atherogenic function of oxLDL, its ability to suppress transcription of CCR2, a monocyte receptor for MCP-1. Once monocytes have migrated to the arterial intima, an environment that can be rich in oxLDL, the loss of CCR2 may favor their accumulation. Because this environment promotes their differentiation to macrophages and, later, to lipid-laden foam cells, the recruitment of monocytes is thought to contribute to vessel pathology. The authors show that monocytes interact with oxLDL primarily through the scavenger receptor CD36, and they argue that uptake of oxidized lipid from the oxLDL particle is required for CCR2 downregulation. Since this effect can be mimicked by providing cells with pure oxidized fatty acids that are ligands for the transcription factor PPARγ, Han et al. tested the effects on CCR2 expression of another known PPARγ agonist, the antidiabetic drug BRL49653 (rosiglitazone). A recent *JCI* paper from some of the same authors showed that rosiglitazone prevents atherogenesis in male mice. Consistent with this finding, the present data show that, both in cultured human monocytes and in vivo in atherosclerosis-prone mice, treatment with rosiglitazone downregulates CCR2. One benefit of the drug may derive from its ability to prevent circulating monocytes from responding to chemokines and being recruited to the arterial intima.

VEGF in hyperoxic lung injury

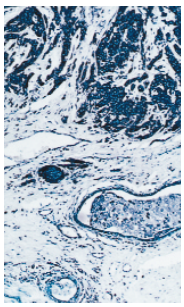
(See article on pages 783–791)



As stressed in several articles in the current *JCI* Perspective series, hypoxia in the lung and other tissues induces VEGF, and treatments that block VEGF signaling impair the normal tissue responses to ischemia. Remarkably, Corne and colleagues now report that VEGF is also beneficial in controlling lung tissue damage in the converse situation of higher-than-normal oxygen concentrations. Mice that breathe pure oxygen for 4–5 days normally die of hyperoxic acute lung injury (HALI), in which pulmonary endothelial cells die and expose the underlying basement membrane of lung capillaries. Following sublethal HALI, endothelial cells proliferate to restore normal capillaries in the lung. VEGF, which is induced by alveolar epithelial cells during this recovery period, undoubtedly contributes to this process, and Corne et al. find that overexpression of VEGF during the period of hyperoxia affords considerable protection, perhaps allowing for continuous repair or replacement of damaged capillaries. Mice carrying an IL-13 transgene survive in pure oxygen about twice as long as controls, and biochemical analysis of bronchioalveolar lavage from hyperoxic transgenic animals shows a dramatic increase in levels of several isoforms of VEGF. VEGF expression is also induced in transgenic mice breathing normal room air, suggesting that these animals are protected from hyperoxic injury even at the beginning of their exposure to pure oxygen. Nevertheless, VEGF expression in transgenic animals differs quantitatively and qualitatively after hyperoxia. Function-blocking antibodies to VEGF reduce but do not eliminate the protective effect of the transgene, leaving open the possibility that some of IL-13's beneficial effects are independent of VEGF.

The Cdc25A protein phosphatase in human breast cancer

(See article on pages 753–761)



Cell cycle regulation goes awry in most cancers, often because one or more cell cycle checkpoints are not induced in tumor cells. Defects in tumor suppressors or oncoproteins allow the cell to speed past these control points and to proliferate at an abnormally high rate. The G1/S checkpoint, which controls entry into the S (DNA synthesis) phase of the cycle, is regulated by the activation of cyclin-dependent kinase 2 (Cdk2) and is frequently missing in tumor cells. Working with an archival panel of carcinoma tissue, Cangi et al. have shown that Cdk2 activity is unusually high in a subset of breast carcinomas but that Cdk2 expression levels are not typically increased. Rather, Cdk2 activation in these samples can be ascribed to two common events: repression of the cdk2 inhibitor p27 or overexpression of Cdc25A, a protein phosphatase that dephosphorylates and thereby activates Cdk2, thus permitting cells to pass the G1/S checkpoint and proceed into S phase. Cangi et al. confirm that cultured mammary tumor cells lose Cdk2 and become blocked at the G1/S checkpoint when treated with an antisense oligonucleotide that interferes with Cdc25A expression. By analyzing records of breast cancer patients in light of their molecular characterization of the archival tumor samples, Cangi et al. show that tumor overexpression of Cdc25A correlates with poor outcome of the cancer, particularly when the tumors also show diminished p27 expression. The molecular basis of Cdc25A overexpression in these tumors is not known and may differ from patient to patient, but since this overexpression appears to generate more aggressive tumors, testing for Cdc25A levels in tumor biopsies may prove helpful in tailoring treatments to individual breast cancer patients.