MECHANISMS OF MICROVASCULAR INFLAMMATION INDUCED BY ALVEOLAR HYPOXIA

BY

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ABSTRACT

Alveolar hypoxia is observed in a number of clinical settings, and is frequently associated with systemic effects, many of which present an inflammatory component. Reduction of alveolar PO_2 in rats induces a rapid and widespread inflammatory response in mesentery, skeletal muscle and brain, characterized by increased microvascular levels of reactive oxygen species (ROS), increased leukocyte-endothelial adhesive interaction, extravasation of albumin and perivascular mast cell degranulation. There is substantial evidence that the systemic inflammation elicited by alveolar hypoxia is not triggered by the reduction of peripheral tissue PO_2, but rather by a mediator(s) released from alveolar macrophages and transported by the circulation. The mediator activates local tissue mast cells which release inflammatory agents and activate the renin-angiotensin system (RAS) to initiate the systemic inflammation.

The major objective of this study was to investigate the links between alveolar hypoxia, alveolar macrophages, resident tissue macrophages and mast cells to understand the mechanisms underlying the systemic inflammation.

Our results showed that topical application of supernatant of hypoxic alveolar macrophages, but not of hypoxic peritoneal macrophages produced inflammation in the normoxic mesentery. Hypoxia induced a respiratory burst in alveolar, but not peritoneal macrophages. Cultured peritoneal mast cells did not degranulate with hypoxia. Immersion of mast cells in supernatant of hypoxic alveolar macrophages, but not in supernatant of hypoxic peritoneal macrophages, induced mast cell degranulaton.. These data suggest that alveolar macrophage-

borne mediator activates mast cells and triggers the systemic inflammation induced by hypoxia, in which reduced systemic PO_2 and activation of tissue macrophage do not play a role.

Hypoxia induced release of monocyte chemoattractant protein-1(MCP-1/CCL-2), a mast cell secretagogue, from alveolar macrophages, but not peritoneal macrophages or mast cells. Further studies showed that alveolar macrophage-borne MCP-1 played a central role in the inflammation: 1) Alveolar hypoxia produced a rapid increase in plasma MCP-1 concentration of conscious intact rats, but not of alveolar macrophage-depleted rats. 2) Degranulation occurred when mast cells were immersed in the plasma of hypoxic intact rats, but not of alveolar macrophage-depleted rats. 3) MCP-1 added to normoxic rat plasma and supernatant of normoxic alveolar macrophages produced concentration-dependent degranulation of immersed mast cells. 4) MCP-1 applied to the mesentery of normoxic intact rats replicated the inflammation of alveolar hypoxia. 5) The CCR2b receptor antagonist RS-102895 prevented the mesenteric inflammation of alveolar hypoxia in intact rats. Additional data suggested that a co-factor constitutively generated in alveolar macrophages and presented in normoxic body fluids is necessary for MCP-1 to activate mast cells at biologically relevant concentrations.

As previously seen in cremaster, the RAS is involved in the mesenteric inflammation of hypoxia. Demonstration of similar inflammatory pathways in both cremaster and mesentery provides further support to the idea of a circulating mediator initiating the inflammation of hypoxia. The previous findings in the

cremaster were expanded in several ways: an involvement of NADPH oxidase as an RAS effector was shown. In addition, it was demonstrated that renin is expressed in rat peritoneal mast cells, and that renin from MCP-1/CCL2-activated mast cells contributes to activation of tissue-specific RAS in inflammation induced by alveolar hypoxia.

In summary, the present studies provide substantial evidence in support of the idea that the systemic inflammatory response to alveolar hypoxia is initiated by an alveolar macrophage-borne MCP-1, which, in turn, activate local RAS via mast cell-derived renin and initiates the cascade of inflammation.

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