LEUKOCYTES ARE KEY TO THE PRO-THROMBOTIC EFFECTS OF ABACAVIR

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INTRODUCTION

• Abacavir (ABC) has been linked to vascular toxicity but its mechanism of action remains unclear. ABC, a purine analogue, shares structural similarities with endogenous purines (e.g. ATP and ADP, Figure 1), major signaling molecules capable of triggering inflammatory and pro-thrombotic programs by interacting with P2-like receptors on vascular structures.

• ABC induces platelet-leukocyte-endothelial cell interactions and pro-thrombotic effects through a mechanism involving intercellular communication with the purinergic system, specifically with ATP-P2X7 receptors1-4 (Figure 2).

• The recruitment of leukocytes, mainly neutrophils, by platelets is an important phase in the formation of thrombi.

OBJECTIVE

To evaluate the role of white cells in the pro-thrombotic effects of ABC in an animal model of thrombosis.

METHODS

• Mouse strains used: C57BL/6 Wild-type (WT).

Model of leukopenia

• Leukopenia was induced by cyclophosphamide (CPM, 150 mg/kg, i.p., 96 h).

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• Kimura and Wright staining were employed to quantify total leukocytes and neutrophils.

Model of thrombosis

• Thrombosis was induced with the endothelium damaging agent Ferric chloride (FeCl3) at a concentration of 25 mM, which does not modify blood flow but predisposes arterioles to thrombosis in the presence of other deleterious vascular agents.

• Rofecoxib, a selective COX-2 inhibitor and a well characterized vascular P2X7 receptor agonist, was used as positive control.

• The recruitment of leukocytes, mainly neutrophils, by platelets is an important phase in the formation of thrombi.

RESULTS

1. ABC induced dose-dependent vessel occlusion in non-leukopenic mice.

2. CPM reduced the number of leukocytes by almost 90%.

3. The pro-thrombotic effects of ABC were absent in leukopenic mice.

REFERENCE