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 pro-inflammatory and pro-thrombotic programs by interacting with P2A-nucleotide receptors on vascular structures.

- ABC induces platelet-leukocyte-endothelial cell interactions and pro-thrombotic effects through a mechanism involving interference of the purinergic system, specifically with ATP-P2X7 receptors (5-7) (Figure 2).

- The ATP-P2X7 receptors implicated in the leukocyte-endothelial cells interactions induced by ABC are located primarily in leukocytes.

- 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: CypBL/J Wild-type (WT).
- Model of leukopenia
  - Leukopenia was induced by cyclophosphamide (CPM, 150 mg/kg, i.p., 76 h).
  - Kimura and Wright staining were employed to quantify total leukocytes and to differentiate leukocyte populations, respectively.
- 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.
  - Refocuss, a selective CDX2 inhibitor and a well-characterized vascular deleterious vascular effects, was used as positive control.

REFERENCES

3. CypB12/FeCl3 ABC 0.1mg/kg, i.p.

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.

CONCLUSION

The pro-thrombotic effect of ABC in vivo depends on the presence of leukocytes, thus demonstrating a key role of these cells in the deleterious vascular effects of this drug. These results support previous research suggesting that ABC induces thrombosis through a specific mechanism involving leukocyte purinergic P2X7 signaling. This may explain the cardiovascular toxicity associated with the use of ABC in humans.