PCSK9 is a co-activator of platelet function beyond its role in cholesterol homeostasis


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Declaration of interest

- I have nothing to declare
Background

• **PCSK9** plasma levels predict recurrent **cardiovascular events** in stable angina (SA⁺) patients.

• PCSK9 contribution to cardiovascular events might be mediated by mechanisms occurring via **unknown LDLR-independent pathways**.

• **Platelets** (PLT) play a key role both in the **progression** and in the acute complications of **atherosclerosis**.
LDLR-independent effects of PCSK9 on platelets
**Background -2**

**Increased platelet reactivity in diabetes**

*Ferroni et al., JTH 2004*

**Platelet abnormalities in patients with diabetes:**

- Increased number of receptors (GpIb, GpIIbIIIa)
- Increased adhesion and activation
- Increased sensitivity to agonists, responding more frequently even to subthreshold stimuli
- Increased epinephrine efflux, sustaining increased platelet activity
- Chronic adrenergic overactivity in diabetes

*Soma et al., Cardiovasc Diabetology 2016*
Background

Increased platelet reactivity in diabetes

Platelet abnormalities in patients with diabetes:

- Increased number of receptors (GpIb, GpIIbIIIa)
- Increased adhesion and activation
- Increased sensitivity to agonists, responding more frequently even to subthreshold stimuli

No study has so far evaluated whether PCSK9 can directly affect platelet function.
Purpose

To evaluate whether:

• PCSK9 modulates platelet activation

• PCSK9 is expressed by platelets from healthy subjects (HS) and stable angina patients, with or without type 2 diabetes mellitus.

Methods

• Effect of PCSK9 on platelet function:
  • epinephrine-induced PLT aggregation (Born aggregometry).
  • whole blood flow cytometry evaluation of P-selectin, PAC-1 and Tissue Factor (TF), platelet-monocytes aggregates.

• PCSK9 expression in platelet and megakaryocytes:
  • flow cytometry
  • Western blot
  • ELISA.
Results

Recombinant PCSK9 lowers the sensitivity of human platelets to epinephrine

PCSK9 is expressed in human megakaryocytes and in a subset of platelets

Platelets from SA patients with T2DM contain twice the amount of PCSK9 compared to the other groups

PCSK9 platelet content

PCSK9 plasma levels
Conclusions

• These findings provide novel knowledge on the mechanisms regulating platelet activation in physiological and pathological conditions.

• Considering the relevance of PLT contribution to cardiovascular disease, these findings shed light on a new mechanism that may be involved in the PLT hyper-reactivity in SA⁺DM⁺ patients.

• Based on our data it is possible that the pharmacological inhibition of PCSK9, besides down-regulating cholesterol levels, may have the added value of controlling the prothrombotic burden interfering with platelet activation.