Title: Platelets facilitate the wound healing capability of mesenchymal stem cells by mitochondrial transfer and stimulation of fatty acid synthesis.

Introduction. Platelets are known to enhance the wound-healing activity of mesenchymal stem cells (MSCs). The 'healing' effects exerted by platelets on MSCs are commonly attributed to the release of growth factors. However, the exact contribution of platelet-released growth factors to MSC activation is unclear since it has never formally demonstrated. Recently, it has been reported that upon their activation, platelets are able to release mitochondria to immune cells to stimulate their pro-inflammatory activities. Here, we explored whether platelet mitochondria can be internalized by MSCs and whether this process contributes to the activation of the MSC's regenerative properties.

Methods. The role of mitochondria transfer from platelets to MSCs was investigated both *in vitro,* following 24 hours-exposure of human MSCs with different concentrations of human platelets or *in vivo,* following the combined delivery of human MSCs and human platelets in mouse cutaneous wounds or dystrophic skeletal muscle.

Results. We found that, upon their activation, platelets transfer respiratory-competent mitochondria to MSCs primarily via dynamin-dependent clathrin-mediated endocytosis. We found that this process enhances the therapeutic efficacy of MSCs following their engraftment in several mouse models of tissue injury including full-thickness cutaneous wound and dystrophic skeletal muscle. By combining *in vitro* and *in vivo* experiments, we demonstrate that platelet-derived mitochondria promote the pro-angiogenic activity of MSCs via their metabolic remodeling. Notably, we show that platelet's mitochondria increase the cytosolic level of citrate in the recipient MSCs leading to the activation of the *de novo* fatty acid synthesis pathway. Finally, we provide evidence that de novo fatty acid synthesis activation is required for increased secretion of pro-angiogenic factors by platelet-preconditioned MSCs.

Conclusion. These results reveal a new mechanism by which platelets potentiate MSC properties and underline the importance of testing platelet mitochondria quality prior to their clinical use.

References

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