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**miR-126 is downregulated in pericytes following exposure to mesenchymal stem cell-derived extracellular vesicles obtained in diabetic-like conditions**

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**Background and aims:** Loss of pericytes in the early phases of diabetic retinopathy (DR) may disrupt their stable association with endothelial cells (EC), leading to EC proliferation and, eventually, angiogenesis. We have recently shown that extracellular vesicles (EV) derived from mesenchymal stem cells (MSC) in diabetic-like conditions may play a role in vessel destabilization by interfering with the strict EC/pericyte/extracellular matrix interactions. Thus they might contribute to angiogenesis through paracrine signalling; in particular, a role for MMP-2 has been described. MicroRNAs (miR) are short RNA sequences acting as gene modulators and playing important roles in angiogenesis and inflammation. MiR-126 is secreted mostly by the endothelium and controls vascular integrity and regeneration after injury. A down-regulation of miR-126 was observed in experimental models of DR, in diabetic retina extracts and in chorioretinal EC in hypoxic conditions, correlating with an increase in VEGF and MMP. Our aim in this study was therefore to investigate miR-126 expression in pericytes and the possible influence of EV derived by MSC cultured in diabetic-like conditions.

**Materials and methods:** Pericytes (HRP) were cultured in physiological (NG), stable high (HG) and intermittent high (intHG) glucose conditions for 8 days. In other experiments, EV were extracted from the supernatant of MSC cultured in hypoxic (hypo) and/or HG conditions and added to HRP cultured in NG for 6, 24 and 48 hrs. Real-Time PCR for miR-126 was performed on RNA extracts.

**Results:** HRP express miR-126 and this expression is down-regulated by 20% in intHG. miR-126 expression is not significantly modified by 6 and 24 hr exposure of HRP to EV. After 48 hrs, miR-126 is up-regulated by exposure to NG-EV (+62% vs ctrl). HG-EV and NG-hypo-EV do not influence significantly miR-126 expression, while EV obtained by MSC cultured in HG + hypoxia (HG-hypo) down-regulate miR-126 (-41% vs ctrl and -64% vs NG-EV,  $p < 0.05$ ).

**Conclusion:** We show for the first time in our knowledge that HRP express miR-126 and that its expression is down-regulated in diabetic-like conditions. Moreover, exposure of HRP to EV obtained in diabetic conditions is able to decrease miR-126 expression, consistently with previous observations of its involvement in DR and providing further insights for our findings of EV contribution to vessel destabilization.

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