

## **SIMVASTATIN ENHANCES VEGF PRODUCTION AND AMELIORATES IMPAIRED WOUND HEALING IN EXPERIMENTAL DIABETES**

Bitto Alessandra<sup>1</sup>, Minutoli Letteria<sup>1</sup>, Altavilla Domenica<sup>1</sup>, Polito Francesca<sup>1</sup>, Fiumara Tiziana<sup>1</sup>, Di Stefano Vincenzo<sup>1</sup>, Daniela Giuliani<sup>2</sup>, Salvatore Guarini<sup>2</sup>, Caputi Achille P.<sup>1</sup> and Squadrito Francesco<sup>1</sup>.

<sup>1</sup>Dept of Exp and Clinical Medicine and Pharmacology, University of Messina and <sup>2</sup>Dept of Biomed Sci, Univ. of Modena and Reggio Emilia, Italy

Statins have different effects beyond cholesterol reduction and stimulate angiogenesis. We investigated the effect of simvastatin in diabetes-related healing defects.

An incisional skin-wound model produced on the back of female diabetic mice (*db<sup>+</sup>/db<sup>+</sup>*) and their normoglycemic littermates (*db<sup>+/+</sup>m*) was used. Animals were treated daily either with simvastatin (40 mg/kg/i.p.) or its vehicle (a 100  $\mu$ l solution of methyl alcohol, DMSO and 0,9% NaCl i.p.). Mice were killed on different days (3, 6 and 12 after skin injury) for measurement of vascular endothelial growth factor (VEGF) mRNA and protein expression, to assess histologically the healing process and to evaluate wound breaking strength and angiogenesis by CD31 and transglutaminase-II immunostaining.

Simvastatin administration in diabetic mice increased VEGF mRNA (simvastatin=  $4.1 \pm 0.6$  n-fold/ $\beta$ -actin; vehicle=  $1.2 \pm 0.3$  n-fold/ $\beta$ -actin) and protein expression (simvastatin=  $6.5 \pm 1$  integrated intensity; vehicle =  $2.3 \pm 0.5$  integrated intensity) and enhanced nitric oxide wound content at day 6. Additionally, the statin augmented breaking strength and CD31 and transglutaminase-II immunostaining at day 12. Finally, simvastatin administration stimulated re-epithelialization and restored the impaired wound healing process in diabetic mice. Similar results were obtained in normoglycaemic mice. Passive immunization with anti-VEGF antibody (10  $\mu$ g/mouse) completely abrogated the beneficial effects of simvastatin on healing in diabetic mice.

Simvastatin has potential application in diabetes-related wound healing disorders.