

Wound Healing Society Annual Meeting May 2002. Baltimore, Maryland

THE S100 PROTEINS MRP8 AND MRP14 ARE ACTIVE AS GENE THERAPY AGENTS IN INCISIONAL WOUND REPAIR.

Jayasri Dasgupta^{*}, Yubin Shi^{*}, Uwe Gossler[†], Wolfgang Hans[†], Michaela Bittner[†], Andreas Goppelt[†] and Jeffrey M Davidson^{*†}. ^{*}Department of Pathology, Vanderbilt University and [†]Research Service, VA Med. Ctr., Nashville, TN and [†]SWITCH Biotech AG, D-82152 Martinsried, Germany (jayasri.dasgupta@mcm.vanderbilt.edu)

Macrophage related proteins or migration inhibitory factor related proteins MRP8 and MRP14 are two members of S100 protein family whose members have two (EF-hand) calcium binding sites per protein chain. They are present in high concentrations in cells of myeloid origin, such as neutrophils and monocytes but not in lymphocytes. These proteins are expressed during myeloid differentiation and expression becomes restricted to granulocytes and monocytes. MRP8 and MRP14 form a heterodimer complex in a Ca²⁺-dependent manner. MRP 8/14 have been found to translocated from the cytosol to the plasma membrane upon neutrophil activation. Many findings suggest that MRP8/14 is involved in regulating the activation of neutrophils and monocytes. MRP8/14 appear to exert some extracellular functions: antimicrobial, cytostatic, and chemotactic activities. Major functions of MRP8/14 is mediation of leukocyte trafficking and response to acute inflammation. Recent findings show that MRP8/14 is upregulated in the epidermis during wound healing, where the complex is both associated with the keratin cytoskeleton and secreted by cultured keratinocytes. To test for a role of these components in wound repair, MRP8 and MRP14 were administered individually or in combination to incisional wounds in normal and diabetic rats using the gene gun (Bio-Rad). In this model, MRP8 alone showed a positive trend in wound breaking strength both in normal (26%, n.s.) and diabetic models (79%, n.s.). MRP14 alone showed less effect in both normal (14%, n.s.) and diabetic models (18%; n.s.). In contrast, the combination of MRP8+MRP14 showed a significant increase in wound breaking strength in normal (76%; p<0.05) but not in diabetic rat incisions (21%). In further support, administration of MRP8 and MRP14 as adenoviral constructs showed a significant increase in wound breaking strength at both d7 (64%; p<0.05) and d10 (27%; p<0.005) in diabetic rats. These results illustrate the utility of functional genomics in the discovery of new vulnerary agents.