MATRIX METALLOPROTEINASES IN SKIN

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Kähäri V-M, Saarialho-Kere U. (1997) Matrix metalloproteinases in skin. *Exp Dermatol* 6: 199-213.

Recent review on the role of matrix metalloproteinases in biology and pathology of skin.

Westermarck J, Kähäri V-M. (1999) Regulation of matrix metalloproteinase expression in tumor invasion. *FASEB J* 13:781-792

Recent review on the role of matrix metalloproteinases in tumor growth and invasion.

Saarialho-Kere UK, Kovacs SO, Pentland AP, Olerud J, Welgus HG, Parks WC (1993) Cell-matrix interactions modulate interstitial collagenase expression by human keratinocytes actively involved in wound healing. *J Clin Invest* 92:2858-2866.

This study shows that migrating keratinocytes in dermal wounds express collagenase-1 (MMP-1), suggesting a role for this MMP in reepithelialization of wounds. Expression of MMP-1 in human epidermal keratinocytes is induced by contact to collagen.

Pilcher BK, Dumin JA, Sudbeck BD, Krane SM, Welgus HG, Parks WC. (1997) The activity of collagenase-1 is required for keratinocyte migration on a type I collagen matrix. *J Cell Biol* 137:1445-1457

This study shows that cleavage of native type I collagen by collagenase-1 is essential for migration of human epidermal keratinocytes on collagen.

Vaalamo M, Mattila L, Johansson N, Kariniemi A-L, Karjalainen-Lindsberg M-L, Kähäri V-M, Saarialho-Kere U (1997) Distinct populations of stromal cells express collagenase-3 (MMP-13) and collagenase-1 (MMP-1) in chronic ulcers but not in normally healing wounds. *J Invest Dermatol* 109:96-101.

Collagenase-3 (MMP-13) is expressed by fibroblasts in chronic human dermal ulcers, but not in normally healing wounds. In addition, MMP-13 is not expressed by migrating keratinocytes in acute or chronic wounds.

Together these3 studies provide evidence for different roles for collagenase-1 (MMP- 1)and collagenase-3 (MMP-13) in human cutaneous wound repair.

Ravanti L, Heino J, López-Otín C, Kähäri V-M. (1999) Induction of collagenase-3 (MMP-13) expression in human skin fibroblasts by three-dimensional collagen is mediated by p38 mitogen-

activated protein kinase. *J Biol Chem* 74:2446-2455.

Collagenase-3 (MMP-13) is expressed by human skin fibroblasts only when they are cultured within collagen gel, but not when cultured in monolayer on plastic. The induction of MMP-13 expression in dermal fibroblasts is dependent on activity of p38 mitogen activated protein kinase. These results provide further evidence for entirely different regulation of the expression of collagenase-1 and collagenase-3 in human skin fibroblasts, suggesting a distinct role for them in biology and pathology.

Fisher GJ, Datta SC, Talwar HS, Wang ZQ, Varani J, Kang S, Voorhees JJ. (1996) Molecular basis of sun-induced premature skin ageing and retinoid antagonism. *Nature* 379:335-9

UVB, even in doses too low to cause erythema induced expression of collagenase-1 (MMP-1), stromelysin-1 (MMP-3), and 92-kDa gelatinase (MMP-9) in normal human epidermis in vivo. Interestingly, induction of MMP-1, MMP-3, and MMP-9 by UVB was potently prevented by topical all-trans-retinoic acid without inhibition of erythema.

Fisher GJ, Wang ZQ, Datta SC, Varani J, Kang S, Voorhees JJ. (1997) Pathophysiology of premature skin ageing induced by ultraviolet light. *New Engl J Med* 337:1419-1428.

A single exposure to UV irradiation results in prolonged induction of collagenase-1 (MMP-1) stromelysin-1 (MMP-3) and gelatinase-B (MMP-9) expression and collagenase and gelatinase activities in human skin. This effect was inhibited by topical retinoic acid.

Together these two reports provide evidence that development of "solar scar" due to repeated exposure to sunlight may be mediated by induction of MMPs by UVB in epidermal keratinocytes.

Liu Z, Shipley JM, Vu TH, Zhou X, Diaz LA, Werb Z, Senior RM. (1998) Gelatinase B-deficient mice are resistant to experimental bullous pemphigoid. *J Exp Med* 188:475-482

This study shows that development of blisters in mouse skin induced by sera from patients with bullous pemphigoid is dependent on the presence of gelatinase B (MMP- 9).

Wang M, Qin X, Mudgett JS, Ferguson TA, Senior RM, Welgus HG. (1999) Matrix metalloproteinase deficiencies affect contact hypersensitivity: stromelysin-1 deficiency prevents the response and gelatinase B deficiency prolongs the response. *Proc Natl Acad Sci U S A* 96:6885-9

Development of contact hypersensitivity in mice requires the presence of stromelysin-1 (MMP-3), whereas clearance of hypersensitivity induced dermatitis is dependent on gelatinase-B (MMP-9).

Together these two papers provide new insight into the role of MMPs in cutaneous inflammation.

Johansson N., J. Westermarck, S. Leppä, L. Häkkinen, L. Koivisto, C. López-Otín, J. Peltonen, J. Heino, and V.-M. Kähäri. 1997. Collagenase-3 (Matrix metalloproteinase-13) gene expression by HaCaT keratinocytes is enhanced by tumor necrosis factor-a and transforming growth factor-b. *Cell Growth Differ* 8:243-250.

Collagenase-3 (MMP-13) is expressed by transformed human epidermal keratinocytes, but not by normal human epidermal keratinocytes in culture.

Johansson N, Airola K, Grénman R, Kariniemi A-L, Saarialho-Kere U, Kähäri V-M. (1997) Expression of collagenase-3 (matrix metalloproteinase-13) in squamous cell carcinomas of the head and neck. *Am. J Pathol* 151:499-508.

Human collagenase-3 (MP-13) is specifically induced in tumor cells of squamous cell carcinomas of the head and neck, and the level of expression correlates with the invasion capacity of the tumors.

Airola K, Johansson N, Kariniemi A-L, Kähäri V-M, Saarialho-Kere U. (1997) Human collagenase-3 is expressed in malignant squamous epithelium of the skin. *J Invest Dermatol* 109:225-231.

Human collagenase-3 is expressed by tumor cells in cutaneous squamous cell carcinomas and basal cell carcinomas, but not by keratinocytes in premalignant lesion of skin indicating that this MMP serves as a marker for keratinocyte transformation.

Johansson N, Vaalamo M, Grénman S, Hietanen S, Klemi P, Saarialho-Kere U, Kähäri V-M. (1999) Collagenase-3 (MMP-13) is expressed by tumor cells in invasive vulvar squamous cell carcinomas. *Am J Pathol*154:469-48

Human collagenase-3 (MMP-13) is specifically expressed by tumor cells in squamous cell carcinomas of vulva, and the expression correlates with the invasion capacity of the tumors.

Together these 4 papers identify collagenase-3 (MMP-13) as a marker for keratinocyte transformation and invasion of squamous cell carcinomas of the head and neck and vulva.

Johansson N, Ala-aho R, Uitto V-J, Grénman R, Fusenig NE, López-Otín C, Kähäri V-M. (1999) Expression of collagenase-3 (MMP-13) and collagenase-1 (MMP-1 by transformed keratinocytes is dependent on the activity of p38 mitogen-activated protein kinase. *J Cell Sci* (In press).

Expression of collagenase-3 (MMP-13), collagenase-1 (MMP-1) and gelatinase-B (MMP-9) in transformed keratinocytes and squamous cell carcinoma cells is dependent on activity of p38 mitogen activated protein kinase (MAPK). In addition, inhibition of p38 activity potently inhibits invasion of transformed keratinocytes through collagen and Matrigel.

Reunanen N, Westermarck J, Häkkinen L, Holmström T, Elo I, Eriksson J, Kähäri V-M. (1998) Enhancement of fibroblast collagenase-1 (MMP-1) gene expression by ceramide is mediated by extracellular signal-regulated and stress-activated protein kinase pathways. *J Biol Chem* 273:5137-5145.

Induction of collagenase-1 (MMP-1) expression in human skin fibroblasts by cytokine-activated ceramide pathway is mediated by coordinate activation of extracellular signal-regulated kinase, Jun N-terminal kinase and p38 mitogen-activated protein kinase pathways.

Together these observations show that p38 MAPK plays an important role in the control of proteolytic activity of cells.

Mattila L, Airola K, Ahonen M, Hietarinta M, Black C, Saarialho-Kere U, Kähäri V-M (1998) Activation of tissue inhibitor of metalloproteinases-3 (TIMP-3) mRNA expression in scleroderma

skin fibroblasts. *J Invest Dermatol* 110:416-421.

Human tissue inhibitor of metalloproteinases-3 (TIMP-3) is expressed at high level in human scleroderma skin fibroblasts in vivo and in culture, suggesting a role for TIMP-3 in dermal fibrosis.

Airola K, Ahonen M, Johansson N, Heikkilä P, Kere J, Kähäri V-M, Saarialho-Kere UK. (1998) Human TIMP-3 is expressed during fetal development, hair growth cycle and cancer progression. *J Histochem Cytochem* 46: 437-448.

Tissue inhibitor of metalloproteinases-3 (*TIMP-3) is expressed by stromal fibroblasts, but not tumor cells in human cutaneous squamous cell carcinomas.*

Ahonen M, Baker AH, Kähäri V-M. (1998) Adenovirus-mediated gene delivery of tissue inhibitor of metalloproteinases-3 inhibits invasion and induces apoptosis in melanoma cells. *Cancer Res* 58:2310-2315.

Adenovirus-mediated expression of TIMP-3 inhibits invasion and promotes apoptosis of malignant melanoma cells in culture. This study identifies TIMP-3 as a novel secreted anti-invasive, anti-angiogenic suicide gene for cancer gene therapy .