Basement Membrane Zone

BMZ Destruction and Remodeling: Understanding Proteases and the Basement Membrane

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doi:10.1038/sj.skinbio.6250017

Looking in the right place with the right assay was the key to discovering collagenase and the first matrix metalloprotease (MMP) in the pregenomic era. Gross and Lapiere (1962) cultured living pieces of metamorphosing tadpole tail in collagen gels and observed lyses of the gel around the fragment, even when the tissue was separated from the collagen by a filter. This suggested that a diffusible protease was produced by living tadpole tissue. Similar studies were conducted with tumor tissue, bone, and human fibroblasts, and so on, also showing collagenase activity. EDTA inhibited cleavage suggesting an MMP and serum also inhibited enzyme activity. Remarkably, collagen was cleaved at a single site, leaving intact $\frac{3}{4}$ and $\frac{1}{4}$ fragments of the molecule. Gross (2004) and Lapiere (2005) have recently revisited their discovery and subsequent events. It is interesting that the tadpole, as well as mice and rats, lack the collagenase 1 (MMP1) gene and utilize other members of the family. The tadpole collagenase 4 gene contains thyroxine response elements, which may coordinate metamorphosis and the resorption of collagen Fujimoto *et al.* (2006).

Lazarus *et al.* (1968), in attempting to explain how collagen was degraded during inflammation, extracted a collagenase stored in human granulocytes (MMP8), which differed in certain properties from the tadpole enzyme. With the discovery of genetically distinct collagens, Liotta *et al.* (1979) found that malignant tumor cells secreted an enzyme (MMP2), which degraded basement membrane (type IV) collagen, but not collagens I, II, III or V. This suggested that the production of this enzyme by malignant tumor cells allowed them to cross basement membrane barriers and disseminate through the body. The requirement for a different collagenase to degrade basement membranes would also allow retention of tissue shape during remodeling and growth. This enzyme has also been referred to as gelatinase A based on its activity in an assay developed by Harris and Krane (1972), which used labeled, denatured collagen to detect proteases in rheumatoid synovial fluid. Indeed, MMP2 cleaves a number of proteins other than collagen IV and a variety of MMPs also degrade collagen IV, dangerous to generalize. The selectivity of certain MMPs as collagenases is likely to relate to their affinity for helical collagens and their ability to unwind a less rigid helical site on the molecule and cleave there, thus attacking their Achilles' heel.

An important development in the genomic era was the isolation of a cDNA clone coding for an MMP having a putative transmembrane domain (membrane type MMP1, mt-MMP1/MMP14) (Sato *et al.*, 1994). Transfection of this MMP cDNA into cells produced an MMP located on the cell surface, demonstrated that it activated proMMP2 and that cells expressing MMP14 had an enhanced ability to migrate through basement membrane barriers. Several such MMPs have now been described and they appear to have many diverse functions, including activating proMMPs secreted by other cells and degrading collagen and other matrix components by direct cell contact.

Much remains unsettled. Why so many MMPs with overlapping activities? Given the great diversity of collagens, do certain MMPs account for the removal of certain collagens? MMP13/collagenase 3 has been implicated in cartilage turnover as well as in rheumatoid arthritis and osteoarthritis (Inada *et al.*, 2004). A variety of MMPS are implicated in tumor growth, spread and during angiogenesis. Cleavage of a portion of laminin 5 was shown to convert it from an attachment factor to a stimulator of migration (Giannelli *et al.*, 1997), with obvious relevance to wound healing and cancer spread. The enzyme mammalian tolloid was shown to be the enzyme in the skin that performs this function in human skin (Veitch *et al.*, 2003).

The MMP system resembles a cascade. Growth requires tissue turnover and the removal of a variety of connective tissue components, which vary from tissue to tissue. Fragments of matrix proteins often have activities of their own, which regulate the process. It is far more complicated than expected and has not yet, but certainly will, yield therapeutic solutions.

TO CITE THIS ARTICLE

Martin GR (2008) BMZ Destruction and remodeling: understanding proteases and the basement membrane. *J Invest Dermatol* 128:E13

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