ONOMY Science

Scientific Journal of Material Science & Engineering

Research Article Open Access

Papers Calprotectin Inhibits Interleukin 1β by Matrix Metalloproteinases by Sequestration of Zinc

Bosgraaf J, Jäger DV and Debra-Borkowski

University of Cambridge, Department of Materials Science and Metallurgy, Pembroke Street, Cambridge CB2 3QZ, England

***Corresponding Author:** Bosgraaf J, University of Cambridge, Department of Materials Science and Metallurgy, Pembroke Street, Cambridge CB2 3QZ, England

Citation: Papers Calprotectin Inhibits Interleukin 1β by Matrix Metalloproteinases by Sequestration of Zinc. Sci J Mat Sci & Eng. 2019; 1(1): 001-008.

Submitted: 09 April 2019; **Approved:** 17 April 2019; **Published:** 22 April 2019

Abstract

Aims: Calprotectin, a 36 kDa protein present in neutrophil cytoplasm, has antimicrobial and apoptosis inducing activities, which are reversed by the addition of zinc. Matrix metalloproteinases (MMPs), a family of zinc dependent enzymes, are important in many normal biological processes including embryonic development, angiogenesis, and wound healing, but also pathological processes such as inflammation, cancer, and tissue destruction. The aim of this study was to investigate whether calprotectin can inhibit MMP activity, and whether such inhibition could be overcome by the addition of zinc.

Methods: MMP activity was measured by the degradation of substrates precoated on to microwells, and visualised by Coomassie blue staining of residual substrate. Seven metalloproteinases (MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, and MMP-13) were tested against two substrates: gelatin and α-casein.

Results: All MMPs except MMP-1 were active against gelatin, whereas MMP-7 was the only enzyme active against α-casein. The addition of calprotectin inhibited the activity of all the MMPs, but different concentrations of the protein, from 0.3μM to > 11μM, were necessary to produce a 50% inhibition of the MMPs. Inhibition by calprotectin was largely overcome by the addition of zinc.

Conclusions: The findings suggest that calprotectin inhibits MMPs by sequestration of zinc. The data also suggest that MMPs have different affinities for zinc and that calprotectin has a lower zinc affinity than the MMPs.

Keywords: Calprotectin; Metalloproteinases; Zinc

INTRODUCTION

Zinc dependent metalloproteinases are important in most aspects of life, from ovulation, embryonic development, and parturition to the development of malignant disease and death.1 Even lower organisms, such as Gram positive and negative bacteria, produce similar enzymes, which can cause tissue destruction directly via activation of our own matrix metalloproteinases (MMPs), or release of membrane anchored cytokines or cytokine receptors.2

Calprotectin, a calcium binding 36 kDa protein constituting more than 60% of total soluble cytosol proteins in human neutrophil granulocytes,3,4 is antimicrobial5–7 probably by means of local zinc deprivation. Sohnle et al have shown recently that calprotectin contains a high affinity zinc binding site, which requires the presence of both types of polypeptide chain.8 It is well known that zinc is vital even for bacteria, and the release of large amounts of calprotectin may contribute to the inhibition of microbial proliferation and the inflammation and tissue destruction that they can cause. Calprotectin can even cause apoptosis in human and animal tumour cells in vitro.9

Our study was designed to test the hypothesis that calprotectin may also inhibit human MMPs, including some involved in tumour invasiveness.10,11 For this purpose, we used the gelatinolytic microwell assay described by Rucklidge and Milne,12 with some modifications. This assay allowed us to test the possible inhibition of MMPs by calprotectin and to test the hypothesis that calprotectin exerts its activity by sequestration of zinc. The use of zymograms (the most common way to test MMP activity) was not an option because the gels contain zinc, whi-

ch was the crucial parameter to be tested.

Materials and Methods

COATING OF MICROWELLS

Stock solutions containing 1 mg/ml of the two substrates were made as follows: 20 mg of gelatin (porcine skin 300 Bloom; Sigma-Aldrich, St Louis, Missouri, USA) was dissolved in 17 ml phosphate buffered saline (PBS), followed by the addition of 3 ml paraformaldehyde (1 mg/ml in PBS). The solution was stirred for 15 minutes at 70°C before use. For α-casein (C-6780; Sigma-Aldrich), 20 mg was dissolved in 16 ml PBS, and 4 ml of paraformaldehyde was added before stirring at 70°C. For coating of microwells (MaxiSorp; Nunc, Roskilde, Denmark), the substrate stock solutions were diluted further in PBS so that by adding 80 µl each well would contain 40 µg gelatin or 50 µg α-casein. The wells were allowed to dry at 51°C for two to three hours in an incubator/dryer IS 80 (Sebia, Issy-les Moulineaux, France), washed four times for 20 minutes with 300 µl distilled water, and stored overnight in distilled water at 4°C. The next day the water was removed, the wells were dried at 37°C for 30 minutes, covered with a plate sealer (Nunc), and stored at −20°C until use.

ACTIVATION OF MMPS

MMPs from R&D systems (Abingdon, UK) were dissolved in TNC buffer (50 mM Tris, 150mM NaCl, 5mM CaCl2, 1µM ZnCl2, 0.01% BRIJ 35, pH 7.6) to give a concentration of 100 µg/ml, and stored at −20°C. MMPs from Chemicon International (Temecula, California, USA) were supplied as frozen liquids, and kept at −20°C until use. The MMPs were diluted in TNC buffer to a stock solution of 4 µg/ml, activated by the addition of 2mM APMA (aminophenyl mercuric acetate) in DMSO (dimethyl sulphoxide), and incubated for 24 hours at 37°C.

TESTING OF MMP ACTIVITY

The activated stock solutions of MMPs were diluted in TNC buffer, containing 0.2mM APMA/DMSO, to give concentrations between 0 and 400 ng/ml, and 200 µl was added to each substrate coated microwell. The wells were covered with a plate sealer and incubated for 22 hours at 37°C.

After incubation, the wells were washed three times for 10 minutes with distilled water and tapped dry.

COOMASSIE BLUE STAINING

Residual substrate was stained by incubation with 0.25% Coomassie brilliant blue (Sigma-Aldrich) in acetic acid/methanol/water (1/10/10 vol/vol/vol) for 30 minutes at room temperature, 200 µl/well. The wells were washed three times for 10 minutes, and once for 30 minutes with distilled water.

To obtain homogenous Coomassie blue staining, residual substrate was brought into solution by the addition of 100 µl 6M HCl, shaking for one to two minutes at 500 rpm, and the addition of 150 µl 2M NaOH. The optical density was read at 595 nm on an Elx800 microplate reader (Bio-Tek instruments, Winooski, Vermont, USA).

INHIBITORY EFFECT OF CALPROTECTIN

Calprotectin, purified from human leucocytes as described by Dale et al,13 was added to give final concentrations of 0–11µM to test for inhibition of MMP activity.

A zinc concentration of 1µM was used in the TNC buffer. This provided enough zinc for the MMPs, and was the concentration recommended for activating the enzymes. To investigate whether an excess of zinc could reverse the effect of calprotectin, a concentration of 100µM was used.

Results

The activated MMPs differed with regard to the degradation of substrates. Despite giving distinct bands on zymogram gels (details not shown), MMP-1 (interstitial collagenase) was inactive against both the substrates in the microwell assay. MMP-2 (gelatinase A), MMP-3 (stromelysin 1), MMP-7 (matrilysin), MMP-8 (collagenase 1), MMP-9 (gelatinase B), and MMP-13 (collagenase 3) were all active against gelatin, whereas MMP-7 was the only enzyme active against α-casein (fig 1). The MMP activities did not vary according to whether they were obtained from R&D systems or Chemicon International.

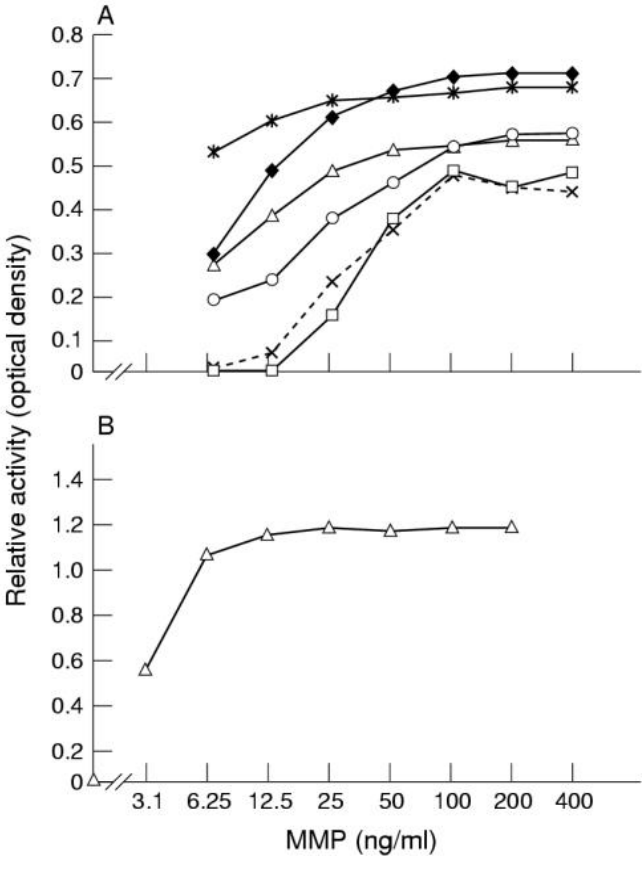

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Figure 1: Degradation of (A) gelatin and (B) casein by matrix metalloproteinases (MMPs). Relative MMP activities against gelatin and casein, at enzyme concentrations ranging from 0 to 400 ng/ml. Closed diamonds, MMP-2; open squares, MMP-3; open triangles, MMP-7; crosses and broken line, MMP-8; asterisks, MMP-9; open circles, MMP-13. The data are expressed as the optical density (OD) at 595 nm for the blank (no enzyme added) minus the OD of the sample wells. Each point represents the mean of duplicates.

INHIBITORY EFFECT OF CALPROTECTIN

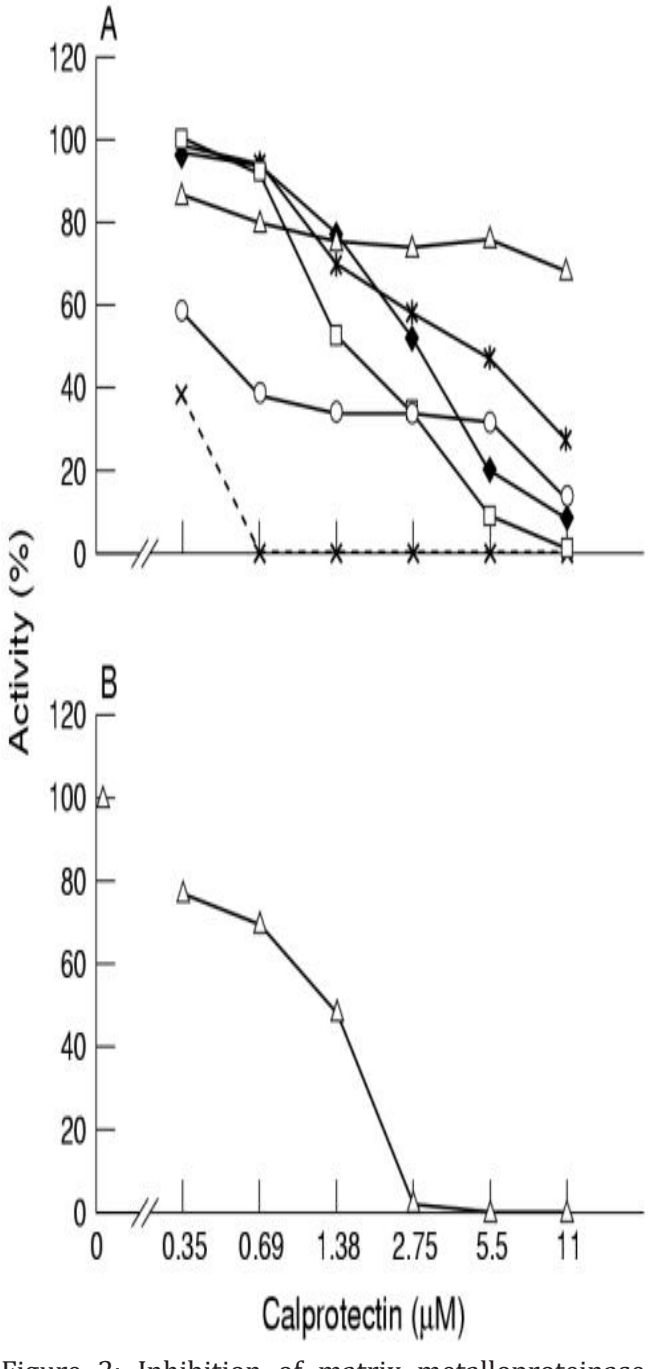

Figure 2: Inhibition of matrix metalloproteinase (MMP) activities by calprotectin in (A) gelatinolytic and (B) caseinolytic microwell assays. Closed diamonds, MMP-2; open squares, MMP-3; open triangles, MMP-7; crosses and broken line, MMP-8; asterisks, MMP-9; open circles, MMP-13. Inhibition is expressed as percentage activity, when 0–11μM calprotectin is present. Each point represents the mean of duplicates.

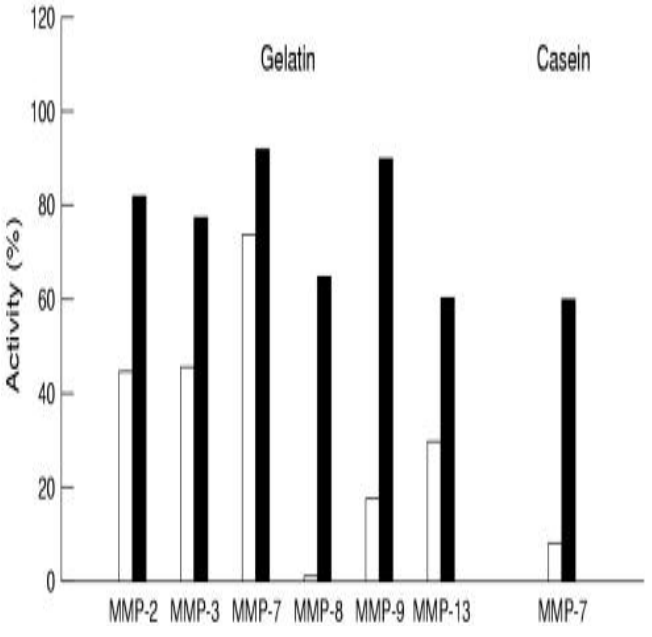

Figure 3: Relative activities of metalloproteinases in the gelatinolytic and caseinolytic microwell assays, when incubated with 11μM calprotectin and 1μM (open bars) or 100μM (closed bars) zinc. The figures are expressed as percentage activity compared with activity without calprotectin.

Discussion

Our results show that modifications of the method described by Rucklidge and Milne allow the quantitative determination of MMP activities. This method avoids the use of radioactive isotopes and different substrates can be used. Furthermore, the assay system is simple and sensitive, allowing detection of 3 ng/ml or less. However, this method is more time consuming than a recently described method using biotinylated gelatin.14 Another aspect is that some substrates, such as collagen, may be altered and less available for enzymatic degradation as a result of the coating process or exposure to paraformaldehyde. For instance, collagen type 1 (from calf skin, Fluka, Buchs, Switzerland) was almost completely converted into gelatin, which was shown by the fact that it was rapidly degraded by trypsin (data not shown).

MMPs are activators of a broad range of cytokines, including interleukin 1, tumour necrosis factor α, Fas ligand, and transforming growth factor β,15–19 and thereby play important roles in regulating processes such as acute and chronic inflammation, tumour cell invasion, apoptosis, and macrophage chemotaxis. Calprotectin may affect various pathophysiological processes by competing with MMPs for zinc. Our study revealed that calprot

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ectin inhibits the activity of all the enzymes tested, and that this inhibition was overcome by the addition of zinc. A higher concentration of calprotectin was necessary to inhibit some metalloproteinases than others, regardless of the substrate. In the gelatinolytic assay, MMP-3, MMP-8, and MMP-13 needed a 200–700 times molar excess of calprotectin to give a 50% inhibition. By comparison, up to a 18 000 times molar excess was necessary to give a similar inhibition of MMP-2 and MMP-9.

These results suggest that MMPs have different affinities for zinc, and that calprotectin has an even lower affinity, because a large excess was necessary for inhibition.

Structurally, MMP-2, MMP-3, MMP-8, MMP-9, and MMP-13 have one catalytic domain containing the zinc binding site. In addition, MMP-2 and MMP-9 have one zinc binding site closer to the C-terminal, suggesting a higher capacity for binding of zinc. MMP-7, the smallest of the proteins, also has one catalytic domain.1 Nonetheless, a much higher concentration of calprotectin was needed to inhibit this enzyme than MMP-3, MMP-8, or MMP-13, which suggests that MMP-7 has a higher affinity constant for zinc.

The metalloproteinases are totally dependent on zinc for their enzymatic activities,1 and our results support the hypothesis that some biological effects of calprotectin are linked to its sequestration of zinc. Sohnle et al showed that calprotectin inhibits microbial activity via a zinc deprivation mechanism,8,20 and it has also been shown that the apoptosis inducing activities of calprotectin were inhibited by the addition of micromolar concentrations of zinc.21 The concentrations of calprotectin needed to inhibit the MMPs in vitro may be biologically relevant. During bacterial infections, up to 120 ng/µl has been found in plasma.4 The release of calprotectin from neutrophils in human peripheral blood may give a concentration of about 20 ng/µl plasma, based on a content of 5 pg calprotectin/cell,22 and 4 × 109 neutrophils/litre blood. Local accumulation of granulocytes corresponding to five times the normal may provide 5µM calprotectin, which would lower the activity of most of the enzymes by 50% or more, if their concentrations in vivo were similar to those used in vitro. The enormous numbers of leucocytes seen at sites of inflammation have the potential to provide several thousand times higher concentrations of calprotectin.

In another USAXS study, the extraordinary sensitivity of the X23A3 USAXS instrument enabled the in situ observation of x-ray scattering from dislocation structures during the deformation of single crystal aluminum [14]. Attempts over the years to measure small-angle scattering from dislocation structures have mostly met with limited success for various reasons. One of the earliest recognized reasons was the intrusion into the data of double-Bragg diffraction. Another problem was surface scattering from improperly prepared surfaces. Finally, unless the scattering vector is nearly perpendicular to a dislocation line, no appreciable scattering is seen. By avoiding double-Bragg diffraction conditions, meticulous sample surface preparation, and by orienting the samples for dislocation visibility, it was possible to observe: 1. correlations in the ordered fraction of dislocations, 2. the presence of dislocation dipoles, 3. the increasing dislocation content with increasing strain, and 4. the decreasing width of the interface between the dislocation walls and the surrounding, nearly-dislocation-free material. In Fig. 5, the increasing dislocation content with increasing strain can be seen directly from the slit-smeared USAXS from single-crystal aluminum at strains of 0.4 %, 0.9 %, 2.2 %, 3.6 %, 4.4 %, 5.3 %, and 6.7 %.

Conclusions

In 1984, NIST's synchrotron facilities were inaugurated with the commissioning of a single beam station at the NSLS for x-ray topography. Today, the combined portfolio of NIST/MSEL facilities with our partners at the NSLS and with UNICAT at the APS offers measurement capabilities in ultra-small-angle x-ray scattering, high-resolution x-ray topography, hard and soft XAFS, and standing-wave x-ray diffraction. It also offers access to leading edge instruments for structural crystallography and time-resolved structural scattering, surface and interface scattering, diffuse scattering and magnetic scattering. The NIST synchrotron facilities enable researchers to use these intense x-ray sources for the advancement of science and technology in materials, physics, chemistry, and, most recently, biology. The primary thrust is the application of leading-edge x-ray scattering and imaging to a broad range of scientific problems and the continued development of novel techniques for innovative research.

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