Effect of the R569W Missense Mutation on the Biosynthesis of Myeloperoxidase*

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William M. Nauseef‡, Melissa Cogley, and Sally McCormick

From the Department of Medicine, Veterans Administration Medical Center and the University of Iowa, College of Medicine, Iowa City, Iowa 52242

The efficient oxygen-dependent microbicidal function of human polymorphonuclear neutrophils (PMNs) depends on the activity of myeloperoxidase (MPO; donor $\mathrm{H}_2\mathrm{O}_2$ oxidoreductase, EC 1.11.1.7) (1, 2), a heme-containing lysosomal protein present in neutrophils and monocytes (2–12). In the presence of $\mathrm{H}_2\mathrm{O}_2$ generated by the NADPH oxidase of stimulated phagocytes, MPO catalyzes the production of hypochlorous acid and other reactive species that are microbicidal and tumoricidal (13, 14). When MPO function is compromised, either by the addition of inhibitors or by using cells deficient in MPO, the killing of bacteria is retarded and that of Candida is absent (2, 15–18). Thus MPO has been assigned a central role in oxygen-dependent, PMN-mediated host defense.

Hereditary deficiency of MPO is relatively common, affecting 1 in every 2,000–4,000 individuals (19). We have previously described a series of unrelated individuals with hereditary MPO deficiency whose PMNs lack spectroscopic and enzymatic evidence of functionally active MPO but possess a 90-kDa protein recognized by a monospecific antibody to MPO (20). Based on these studies, we speculated that this form of MPO deficiency results from synthesis of an aberrant MPO precursor, which is incorrectly processed posttranslationally (20). We have recently reported that a single nucleotide missense mutation in exon 10 of the MPO gene is a common genotype underlying MPO deficiency (21). Based on the amino acid sequence of MPO, one would predict that this mutation results in the substitution of tryptophan for arginine at codon 569 (R569W). The impact of this mutation on MPO biosynthesis is unknown.

In studies using K562 cells transfected with cDNA for normal and for mutated MPO, we describe the effects of the R569W mutation on MPO biosynthesis. These studies demonstrate that the R569W missense mutation results in a maturation arrest in MPO processing at the apopro-form of the enzyme. Furthermore, the data suggest that insertion of heme into the peptide backbone of apopro-MPO may be a prerequisite for proteolytic maturation of pro-MPO.

**EXPERIMENTAL PROCEDURES**

Reagents—Restriction endonucleases and buffers, specific primers for the polymerase chain reaction, and Taq polymerase were obtained from the DNA Core Facility (University of Iowa); reagents for cell culture were obtained from the Hybridoma Facility (University of Iowa); and radiolabeled dNTPs were obtained from Amersham Life Sciences Products.

Vectors and cDNA Constructs—Full-length cDNA for human MPO (22) was donated into the BamHI site of pREP10 (Invitrogen, San Diego, CA) for stable expression in mammalian cells. Site-directed mutagenesis using overlap extension with the polymerase chain reaction (24, 25) was employed to generate the R569W mutation using normal cDNA for MPO in pCMV5 (23) as template. Primers used for mutagenesis were the forward primers $\mathrm{C}_1$ (TGGACGCGCCACCTCCTCATCAACCCCATGTT2370) and $\mathrm{C}_2$ (TTGGATGAGATCTGTAGGAGGGGAGCGATTGTTT1882) and the reverse primers $\mathrm{P}_1$ (CTTGTCCCGAGCTCAGGCTGTTATGGGGTGGGTGT2370) and $\mathrm{P}_2$ (CTTGTCCCGAGCTCAGGCTGTTATGGGGTGGGTGT2370). The nucleotide altered to produce the desired mutation is printed in bold type. The 686-nucleotide amplion was digested with KpnI and the resultant 452-nucleotide fragment cloned into pCMV5-MPO, replacing the fragment of normal sequence (nucleotides 1803–2255) excised with KpnI. The inserted region was directly sequenced on both strands using $3^5\text{-}\text{dATP}$ and the dideoxynucleotide chain termination method (Sequenase, version 2.0, U. S. Biochemical Corp.). The only change in nucleotide sequence produced was the desired mutation (KGG → TGG) at codon 569. The wild-type or mutated cDNA for MPO was excised from pCMV5 and cloned into the BamHI site of pREP10. Plasmids with the correct orientation were expressed in K562 cells.

Transfections—The human cell line K562 (26), was obtained from the American Type Culture Collection (ATCC CCL 245) and maintained in RPMI 1640 with 10% fetal calf serum, 2 mmol/liter glutamine, and...
Lines were biosynthetically radiolabeled with $^{14}$C\(-\text{pREP-MPO}\) and \(\text{pREP-R569W}\) to synthesize pro-MPO, cell-sor pro-MPO (34). In order to assess directly the ability of

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\text{PMNs because of a posttranslational defect in MPO biosynthesis.}
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PMOs related precursor (Fig. 3). However, only \(\text{pREP-MPO}\) synthesized a 90-kDa MPO-related precursor, which was radiolabeled with $^{14}$C\(-\text{a-aminolevulinic acid}\) and consistent with pro-MPO (34). In contrast to the immunoprecipitates from \(\text{pREP-MPO}\) cells, those from \(\text{pREP-R569W}\) cells lacked protein radiolabeled with $^{14}$C\(-\text{a-aminolevulinic acid}\), indicating that these cells did not synthesize pro-MPO. Thus it appears that the R569W mutation results in a maturation arrest in MPO biosynthesis at the apop-MPO stage.

In order to determine if functional heme was incorporated into pro-MPO synthesized by \(\text{pREP-MPO}\), we assayed lysates of wild type K562 cells, \(\text{pREP-MPO}\), and \(\text{pREP-R569W}\) for peroxidase activity (Table I). The parental K562 cells possessed very little peroxidase activity. In contrast, the \(\text{pREP-MPO}\) cells had significantly more peroxidase activity. Thus it appears that K562 cells transfected with normal cDNA for MPO synthesized enzymatically active MPO-related protein. In contrast, \(\text{pREP-R569W}\) cells had very little peroxidase activity, similar to that of wild type K562 cells. Based on these data, we conclude that \(\text{pREP-R569W}\) cells synthesized apop-MPO but were unable to incorporate heme to create pro-MPO. These findings confirm our hypothesis that patients with the R569W genotype of MPO deficiency lack peroxidase activity in their PMNs because of a posttranslational defect in MPO biosynthesis.

- **RESULTS AND DISCUSSION**

The primary translation product for MPO is a single 80-kDa polypeptide, which undergoes cotranslational, N-linked glycosylation to generate a 92-kDa glycoprotein that is processed by glucosidases to produce a relatively long-lived 90-kDa precursor (3-11). The 90-kDa, enzymatically inactive apopro-MPO is converted to the 90-kDa pro-MPO by the insertion of heme. Although the events associated with the conversion of apopro-MPO to a precursor with peroxidase activity have not been completely defined, there is evidence that incorporation of heme is necessary for the proteolytic processing of pro-MPO into the subunits of mature MPO.

- **Transfection of K562 Cells with Normal MPO cDNA**—We selected K562 cells for expression of MPO cDNA because they are of hematopoietic origin (31, 32) and lack MPO (26). The wild type K562 cells electroporated with salmon sperm DNA did not produce MPO and only cells electroporated with cDNA encoding for MPO synthesized a radiolabeled 90-92-kDa protein immunoprecipitated with the monospecific antisera for MPO (data not shown). However, the relatively low MPO expression in transfected cells precluded use of the transient expression system for our studies. In order to study in greater detail the processing of normal MPO precursors and the effect of the R569W missense mutation on MPO biosynthesis, we established stable transfecnts in K562 cells expressing normal and the R569W cDNA for MPO.

Hygromycin-selected transfecnts expressing normal MPO (\(\text{pREP-MPO}\)) synthesized and secreted an MPO precursor (Fig. 1, panel a). As previously shown in cells that naturally express the MPO gene (33), tunicamycin resulted in biosynthesis of a nonglycosylated 80-kDa protein that was not secreted (Fig. 1, panel b).

K562 cells stably expressing cDNA with the missense mutation at codon 569 (\(\text{pREP-R569W}\)) were similarly pulse-labeled. When analyzed by immunoprecipitation of the cell lysate after the pulse labeling and was gradually secreted into the medium during the chase period. Panel b, when \(\text{pREP-MPO}\)-transfected cells were grown in the presence (+TM) of tunicamycin (6.1 $\mu$M), the immunoprecipitated protein migrated at 80 kDa, in contrast to the 90-kDa size made in the absence (–TM) of tunicamycin. In addition, the nonglycosylated 80-kDa protein was not secreted during the chase period.

- **Comparison of biosynthesis of MPO-related precursors by stably transfected K562 cells expressing normal (\(\text{pREP-MPO}\)) and mutated (\(\text{pREP-R569W}\)) cDNA for MPO.** Transfectants pulse-chase labeled with $^{35}$S\(-\text{methionine}\) were analyzed as described in the legend to Fig. 1. \(\text{pREP-R569W}\)-transfected cells synthesized a 90-kDa protein related to standard cDNA made by \(\text{pREP-MPO}\)-transfected cells, cells expressing the normal cDNA for MPO. Similarly, the 90-kDa MPO-related precursor protein was secreted into the cell media of both cell lines over a similar time course.

- **Effects of R569W Missense Mutation on MPO Biosynthesis**

| MEDIUM | CELL | CELL | MEDIUM |
|--------|-----|-----|--------|
| 90-kDa | 0   | 3   | 0      |
| 80-kDa | 20  | 20  | 0      |

**FIG. 1.** Stable expression of MPO-related proteins by \(\text{pREP-MPO}\)-transfected K562 cells. Hygromycin-selected K562 cells stably expressing \(\text{pREP-MPO}\) were pulse-labeled with $^{35}$S\(-\text{methionine}\) and chased for the indicated time periods. At the specific periods of chase, cell lysates and culture media were collected and immunoprecipitated with monospecific antisera against MPO and the immunoprecipitated proteins separated by SDS samples by \(\text{pREP-MPO}\)-gel electrophoresis and visualized by autoradiography. Panel a, a 90-kDa protein was immunoprecipitated from the cell lysate after the pulse labeling and was gradually secreted into the medium during the chase period. Panel b, when \(\text{pREP-MPO}\)-transfected cells were grown in the presence (+TM) of tunicamycin (6.1 $\mu$M), the immunoprecipitated protein migrated at 80 kDa, in contrast to the 90-kDa size made in the absence (–TM) of tunicamycin. In addition, the nonglycosylated 80-kDa protein was not secreted during the chase period.
In order to distinguish heme-containing pro-MPO from proapo-MPO, cells expressing pREP-MPO and those expressing pREP-R569W were radiolabeled with \(^{14}C\)-labeled methionine and processed to mature, enzymatically active mature MPO. Thus it appeared that K562 cells could synthesize pro-MPO and therefore express heme-containing MPO-related precursor, although both pREP-MPO and pREP-R569W cells synthesized 90-kDa MPO precursor protein.

### Proteolytic Processing of MPO Precursors in pREP-MPO and pREP-R569W—

Native MPO is a symmetric, heterodimeric protein, each half composed of 59-kDa and 13.5-kDa subunits (33). Studies have suggested that proteolytic processing to the lysosomal form may require incorporation of heme into the precursor (35–37) (i.e. when heme incorporation is blocked by succinyl acetone, an inhibitor of heme synthesis (38), pro-MPO does not undergo proteolytic processing to the lysosomal form of native MPO).

When pREP-MPO cells were pulse-labeled and chased for 20 h, the 59-kDa heavy subunit of lysosomal MPO was detected within the cells (Fig. 4), demonstrating that K562 cells have the capacity to process pro-MPO into mature protein. On the other hand, pREP-R569W cells pulse-chase-labeled under identical conditions did not generate the subunits of mature MPO. Thus it appeared that K562 cells could synthesize pro-MPO and process it to mature, enzymatically active mature MPO when transfected with cDNA encoding normal MPO. However, the form of apo-MPO made in pREP-R569W cells could not undergo proteolytic processing to mature MPO.

### Proteolytic processing of pro-MPO to MPO in pREP-MPO and pREP-R569W—

Properties of MPO precursors in pREP-MPO and pREP-R569W—

Proteolytic processing of the MPO precursor to mature MPO in pREP-MPO and pREP-R569W transfected K562 cells. Stable cell lines expressing pREP-MPO (MPO) or pREP-R569W (R569W) were pulse-labeled, chased for 20 h, and the lysates immunoprecipitated with antisera to MPO (mMPO). As in myeloid cells expressing endogenous cDNA for MPO, the pREP-MPO-transfected cells synthesized and processed the 90-kDa MPO precursor into mature, lysosomal MPO, containing a heavy subunit of 59 kDa. In contrast, pREP-R569W-transfected cells failed to process the MPO precursor into the subunits of mature MPO.

### Effects of R569W Missense Mutation on MPO Biosynthesis

First, studies using the pREP-R569W cell line demonstrate that the R569W missense mutation resulted in a “maturational arrest” in the processing of MPO precursors at the stage of apo-MPO. Presumably an identical mutant apo-MPO is the immunoreactive 90-kDa protein previously identified in the neutrophils of subjects with hereditary MPO deficiency and the R569W genotype (20, 21). Thus these findings confirm our hypothesis that the R569W missense mutation results in a defect in the posttranslational processing of MPO (20).

Second, the K562 cells stably transfected with the cDNA for normal MPO demonstrated many of the features seen during the biosynthesis of MPO in myeloid cells. The pREP-MPO cells synthesized apo-MPO, incorporated heme to make pro-MPO and processed pro-MPO into the mature, lysosomal form of the protein. This is in contrast to previous studies using Chinese hamster ovary cells (39–41), baby hamster kidney cells (42), or baculovirus-infected Sf9 cells (43) to express MPO cDNA. In none of these systems were all three species, namely apo-MPO, pro-MPO, and mature active MPO, produced. Thus the K562 cell line provides a mammalian cell line of hematopoietic origin suitable for examination of the biosynthesis of heme-

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**TABLE I**

| Cell line       | No hemin | Hemin added |
|-----------------|----------|-------------|
| K562            | 0.58 ± 0.04 (4) | 0.62 ± 0.04 (6) |
| pREP-MPO        | 1.57 ± 0.04 (5)  | 3.54 ± 0.21 (6) |
| pREP-R569W      | 0.60 ± 0.02 (4)  | 0.59 ± 0.01 (6) |

* a Versus K562 cells (p < 0.000001).
* b Versus K562 cells (p < 0.000006); versus pREP-MPO cells without hemin (p = 0.00002); versus pREP-R569W cells with hemin (p = 0.000003). c Versus K562 cells; not a statistically significant difference (p = 0.4).

**TABLE II**

| pREP-MPO | pREP-R569W |
|----------|------------|
| 90-kDa   | 59-kDa     |
| 90-kDa   | 59-kDa     |

| - Hemin | 1.00 1.00 |
| + Hemin | 0.62 2.57 |

**Fig. 3.** Synthesis of pro-MPO by pREP-MPO and by pREP-R569W-transfected K562 cells. In order to distinguish heme-containing pro-MPO from proapo-MPO, cells expressing pREP-MPO and those expressing pREP-R569W were radiolabeled with \(^{14}C\)-labeled methionine (35–37) and MPO-related proteins similarly immunoprecipitated. Only pREP-MPO-transfected cells synthesized a heme-containing MPO-related precursor, although both pREP-MPO and pREP-R569W cells synthesized 90-kDa MPO precursor protein.

**Fig. 4.** Proteolytic processing of the MPO precursor to mature MPO in pREP-MPO- and pREP-R569W-transfected K562 cells. Stable cell lines expressing pREP-MPO (MPO) or pREP-R569W (R569W) were pulse-labeled, chased for 20 h, and the cell lysates immunoprecipitated with antisera to MPO (mMPO). As in myeloid cells expressing endogenous cDNA for MPO, the pREP-MPO-transfected cells synthesized and processed the 90-kDa MPO precursor into mature, lysosomal MPO, containing a heavy subunit of 59 kDa. In contrast, pREP-R569W-transfected cells failed to process the MPO precursor into the subunits of mature MPO.

**Fig. 5.** Effects of exogenous hemin on proteolytic processing of the MPO precursor to mature MPO. Cells transfected with pREP-MPO or pREP-R569W were pulse-labeled and chased for 20 h in the absence (–) or presence (+) of added hemin (2 μg/ml). The proteolytic processing of the MPO precursor to mature MPO (represented by the 59-kDa heavy subunit) was augmented 2.5-fold by the addition of hemin. In contrast, the defect in proteolytic processing seen in the cells expressing pREP-R569W persisted even in the presence of added hemin.

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\(^{2}\) W. M. Nauseef, unpublished data.
containing myeloid proteins.

Third, in addition to the implications of these findings to understanding the biochemical basis of one of the genotypes underlying hereditary MPO deficiency, our studies using the stable K562 transfectants support and extend previous suggestions that heme insertion is necessary for proteolytic processing of pro-MPO into the subunits of mature MPO (35–37). Exposure of promyelocytic cells to succinyl acetone, an inhibitor of heme synthesis, blocks proteolytic processing of MPO precursors to mature MPO and this inhibition is reversed by inclusion of hemin in the culture medium. Pinnix et al. (37) demonstrated that succinyl acetone did not alter mRNA for MPO in treated cells and speculated that heme was essential for the maturation of MPO precursors in the endoplasmic reticulum. In support of that conclusion, pREP-MPO cells possessed more peroxidase activity and synthesized more mature MPO in the presence of hemin. The pREP-R569W cell line, which was unable to incorporate heme and could synthesize only appropMPO, was unable to process proteolytically the MPO precursor into the subunits of mature MPO.

Taken together, data from the studies presented provide an experimental framework for characterization of additional features of normal synthesis, processing, and lysosomal targeting of MPO. It is clear that there is molecular heterogeneity underlying MPO deficiency (44), and this system may be useful for identifying specific events in MPO expression which are abnormal in other genotypes of the disorder, including pre-translational (45) as well as post-translational defects (21, 46). On a larger scale, this expression system may be applicable for the study of biosynthesis of other heme-containing proteins.

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