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Diverse proteins homologous to inositol monophosphatase

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Bovine inositol monophosphatase (IMP) and several homologous proteins were found to share two sequence motifs with bovine inositol polyphosphate 1-phosphatase (IPP). These motifs may correspond to binding sites within IMP and IPP for inositol phosphates or for lithium, since both substances are bound by these proteins. This suggests that the proteins homologous to IMP, which have diverse biological roles but whose function is not clear, may act by enhancing the synthesis or degradation of phosphorylated compounds.

Amino acid sequence; Inositol phosphate; Signaling pathway

We have found several proteins homologous to the inferred amino acid sequence of bovine inositol monophosphatase (IMP) [1], an enzyme of the inositol phosphate second messenger signaling pathway [2].

A search of the PIR protein database (release 28.0) using the FASTA program of Pearson and Lipman [3] yielded homologies between IMP and 2 inferred *Escherichia coli* proteins: the products of the *suhB* and *amtA* genes, mutations which result in enhanced synthesis of the heat shock transcription sigma factor [4], and deficiency in ammonium transport [5], respectively. Homologies between IMP and the products of the *Neurospora crassa qa-x* [6] and *Aspergillus nidulans qutG* [7] genes, which are both part of a cluster of genes involved in quinic acid utilization, have been reported previously [1]. A search of the GenBank database (release 67) using the FASTA program [3] uncovered a fifth homology to an open reading frame (ORF) upstream from the *pss* gene of *Rhizobium leguminosarum* [8] which is required for exopolysaccharide (EPS) synthesis and nodulation of peas. (Only the 3′ end of the sequence is known since the 5′ end of this ORF was deleted during cloning of the fragment.)

A well conserved motif within these proteins, defined as W-x̄-[IV]-D-P-[IL-D-G-T-x̄(2)-[FY]-x̄-[HK] (motif A, Fig. 1), was compared to sequences in the PIR and the translated GenBank databases using a UNIX lexical analysis program [9]. At most, 1 insertion or deletion at a variable residue (x̄) and 1 substitution at a consensus residue was allowed. An exhaustive search yielded only 1 additional protein with this motif, bovine inositol polyphosphate 1-phosphatase (IPP) [10], which also contains a second motif defined as W-D-x̄(2)-[AG]-[AG]-x̄-[AIL]-[ILV]-[ALV]-x̄(3)-G-[AG] (motif B). Based on differences in the consensus pattern when the IPP sequence is included, motif A was redefined as W-x(0,1)-[IV]-D-P-[IL]-D-x-T-x(2)-[FY]-x-[HK]. These motifs may correspond to binding sites within IPP and IMP for inositol phosphates or for lithium since both proteins are inositol phosphate phosphatases and are uncompetitively inhibited by lithium (see references in [2,10]).

What do these homologies tell us? The extensive homology to IMP and the presence of 2 motifs similar to patterns found in IPP suggest that the homologous proteins are related to these phosphatases. Perhaps these proteins are components of a signaling pathway. The findings that *suhB* is probably identical to the *ssyA* gene [4], which was identified as an extragenic suppressor of a mutation affecting protein secretion, and that *amtA* is identical to the *cysQ* gene, which is required for efficient biosynthesis of cysteine (Neuwald et al., unpublished), suggest a pleiotropic role for these genes. This, along with preliminary evidence linking the *qa-x* gene to catabolite repression [11], raises the possibility that these proteins act by enhancing the synthesis or degradation of phosphorylated messenger molecules as adenylate cyclase and phosphodiesterases act in the synthesis or degradation of cyclic AMP, a signal for catabolite repression in *E. coli*.

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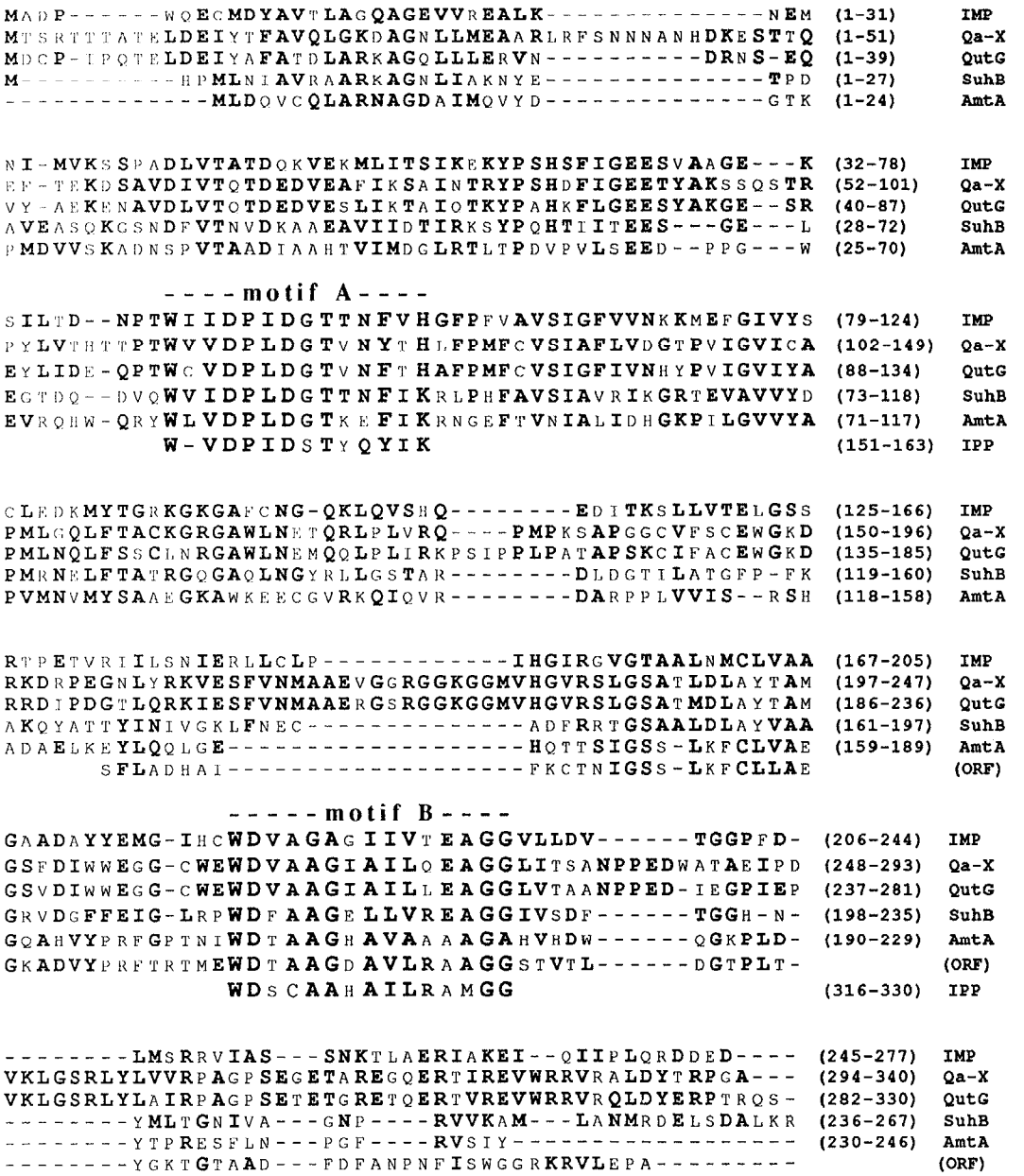

Fig. 1. Conserved regions between inositol monophosphatase and homologous proteins. Similar residues are bold. Comparison of bovine inositol monophosphatase (IMP) to the products of the *Neurospora crassa qa-x* gene (Qa-X) [6], the *Aspergillus nidulans qutG* gene (QutG) [7] and the *Escherichia coli suhB* (SuhB) [4] and *amtA* [5] genes (AmtA), and to the C-terminal peptide fragment inferred from the 3′ end of an ORF upstream from the *Rhizobium leguminosarum pss* gene [8] yielded homology scores of 27, 35, 43, 21 and 10 s.d. units, respectively. Additional comparisons yielded homology scores of 139 (QutG, Qa-X), 18 (SuhB, Qa-X), 23 (SuhB, QutG), 13 (AmtA, Qa-X), 16 (AmtA, QutG) and 28 (AmtA, SuhB) s.d. units. Scores were calculated by computing optimized alignments of one of the protein sequences with 1000 random permutations of the other sequence using the RDF2 program of Pearson and Lipman [3]. IMP and bovine inositol polyphosphate 1-phosphatase (IPP) are not homologous (score: 2.5 s.d. units) but they share 2 motifs (A and B).

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