Discussion Letter

Hydrophobic cluster analysis reveals duplication in the external structure of human α-interferon receptor and homology with γ-interferon receptor external domain

Christine Gaboriaud[1,*], Gilles Uzé[2], Georges Lutfalla[2], and Knud Mogensen[2]

[1]*Laboratoire de Minéralogie-Cristallographie, CNRS UA09, Universités P6 et P7, T16, 4 Place Jussieu, 75252 Paris CEDEX 05, France* and [2]*Laboratoire d'Oncologie Virale, IRSC, CNRS UPR 274, 7 Rue Guy Môquet, BP 8, 94801 Villejuif CEDEX, France*

Received 22 May 1990

Evidence is presented, based on sequence comparison according to Hydrophobic Cluster Analysis, of a structural and evolutionary relationship between the human α/β-interferon receptor and the human and mouse γ-interferon receptor. These results predict that the human α/β-interferon receptor extracellular part is organised in two homologous subdomains connected by a proline linker. They also predict that both subdomains present some homologies to the external domain of mouse and human γ interferon receptor.

Interferon receptor; Amino acid sequence comparison; Protein homology

1. INTRODUCTION

Immunological studies have classified interferons into three families: α, β and γ. Interferons α and β that share some structural similarities [1] bind to the same specific receptor [2] but γ-interferon binds to another receptor [3]. The primary amino acid sequences of the human α/β-interferon receptor and the human and mouse γ-interferon receptors have been deduced from the sequences of the respective cDNAs [4–6]. The human and mouse γ-interferon receptors are similar in size but are much smaller than the human α/β-interferon receptor. Automatic alignments using classical programs are difficult in this case. For that reason, we used Hydrophobic Cluster Analysis [8] to compare the structural organisation of those receptors. Using this technique, the signal peptide and the transmembrane domain are easily recognized and the proteins can be divided into extracellular and intracellular domains. It is then possible to analyse possible similarities between individual domains. As the extracellular domain of the human α/β-interferon receptor is twice as large as the corresponding domain of the γ receptors, we checked the possibility of an internal duplication in this part of the α/β receptor. We show here that it is possible to consider the extracellular domain of α/β interferon receptor as a duplication of the extracellular domain of the γ receptor.

Correspondence address: G. Lutfalla, Laboratoire d'Oncologie Virale, IRSC, CNRS UPR 274, 7 Rue Guy Môquet, BP 8, 94801 Villejuif Cedex, France

* *Present address:* Laboratoire de cristallographie, Institut de Chimie des Substances Naturelles, CNRS, 91198 Gif/Yvette Cedex, France

2. INTERNAL DUPLICATION IN THE EXTRACELLULAR DOMAIN OF THE HUMAN α/β-INTERFERON RECEPTOR

Hydrophobic cluster analysis (HCA) was carried out as described by Gaboriaud et al. [7] by plotting the sequence on a classical α-helix and spreading it to two dimensions. We took advantage of a central stretch of prolines in the middle of the extracellular part of the human α/β-interferon receptor to split it in two domains. This was suggested to us by the case of rhodanese (thiosulfate sulphurtransferase) where the two structurally related domains are separated by a proline linker [7]. Alignments are then made between those subdomains according to the similarities in the cluster patterns. Segmentation by prolines, glycines and hydrophilic areas are also used as a criterion for alignment. A linear version is presented in Fig. 1A (copies of the HCA plots are available on request). The hydrophobic residues in the cluster patterns used for the alignment are marked with a diamond; identities are boxed and other similarities of type dotted. Cluster analysis provides good evidence for an insertion between residues 264 and 273. This gives 25% of identical

Published by Elsevier Science Publishers B.V. (Biomedical Division)
00145793/90/$3.50

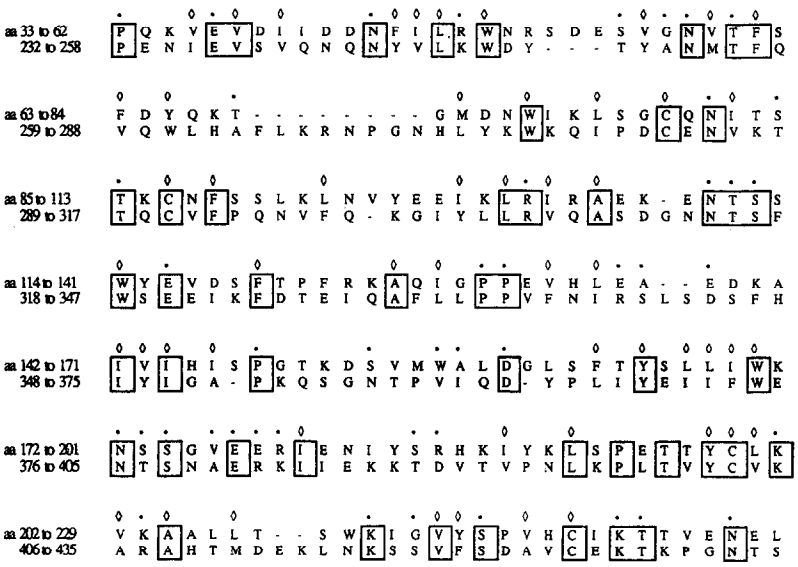

Fig. 1. Linear sequences established from conservation of the hydrophobic cluster pattern. Homology of α-interferon receptor domains. The signal peptide covers residues 1–27 and the transmembrane peptide starts at 437. Diamonds mark residues appearing in conserved hydrophobic patterns. Identities are boxed. Dots indicate residue type similarities.

residues. Cysteines are well conserved and there is a 50% homology between aromatic residues that are important elements of the structure determining the hydrophobic core of the proteins, with 8 out of 11 tryptophans appearing as homologous pairs. The main differences and insertions appear in rather hydrophilic regions between the hydrophobic clusters. They probably correspond to outer parts of the subdomains. The fact that hydrophobic clusters are short and vertical on the plot and that they are composed of alternating hydrophobic/hydrophilic/hydrophobic residues suggest that the core of the subdomains would be made of β-sheets [7].

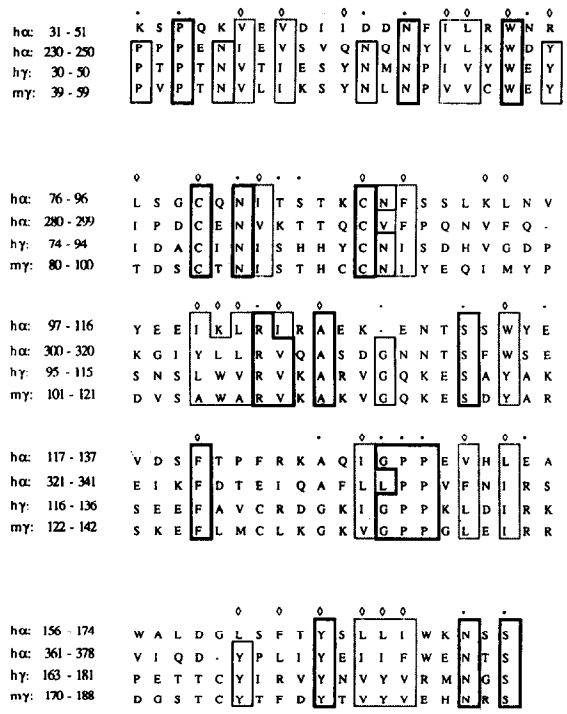

Fig. 2. Fragments of homology appearing between the human (h) and mouse (m) γ-interferon receptor and the human α/β-interferon receptor subdomains. Identities between the four sequences are heavily boxed, identities between three out of four sequences are boxed, type similarities among hydrophobic residues are lightly boxed. Diamonds mark residues appearing in conserved hydrophobic patterns. Dots indicate residue type similarities.

3. EACH SUBDOMAIN OF THE EXTRACELLULAR PART OF THE α/β-INTERFERON RECEPTOR PRESENTS HOMOLOGIES WITH THE EXTRACELLULAR DOMAIN OF THE γ-INTERFERON RECEPTOR

The alignment of the two subdomains of the extracellular part of the human α/β-interferon receptor deduced from the Hydrophobic Cluster Analysis was used to look for homologies with the extracellular domains of human and mouse γ-interferon receptor extracellular domains. We tried to fit the two γ-interferon receptor sequences on the alignment shown in Fig. 1. This alignment shows significant homology in three regions, amino acids 31–51, amino acids 76–137 and amino acids 156–174 according to the numbering of the first subdomain of the human α/β-interferon receptor extracellular domain. Those three stretches of significant homology are shown in Fig. 2. They cover approximately 50% of the primary sequence of each domain. They indicate a conservation of more than 20% between α/β- and γ-interferon receptors if similarities of type are included. Alignment of the four sequences outside those stretches seems less relevant except around

the cysteines at the end of the domains where some local alignments can be obtained [8] but do not indicate a convincing homology.

4. CONCLUSION

There is clearly a duplication in the extracellular part of the human α/β-interferon receptor. The similarities in hydrophobic clustering that we describe for the α receptor suggest that the duplication extends to the secondary and tertiary structure of these domains. However, it is necessary to introduce rearrangements at the extremities of the domains to accommodate the linking of the two domains. This would explain why the two subdomains of the α/β-interferon receptor have diverged. The similarities with the γ-interferon receptors indicate that the interferon receptors share structural homology and reinforce the possibility of similarities in the three-dimensional structure of α-, β- and γ-interferons [9,10]. This also suggests that those receptors evolved from a common ancestor.

Interestingly enough, the different α-interferon subtypes have different specific activities on human cells, but all have the same high specific activity on bovine cells [11]. On murine cells, some α-interferon subtypes have no activity, some have a low specific activity [11]. In that context, the duplication in the extracellular part of the human α/β-interferon receptor could have particularly interesting biological implications. For that reason, the determination of the functional role of this duplication needs the analysis of a larger sequence family including the sequence of the murine and bovine α/β-interferon receptors. This analysis could also be used for the attribution of structural and functional roles to the conserved amino acids we have described.

Acknowledgements: We thank Dr I. Gresser for his constant encouragement. This work was supported by grants from Association pour la Recherche sur le Cancer; Fondation pour la Recherche Médicale; Centre National de la Recherche Scientifique; DRET 89-34-132; ANVAR 8906303 QAT.

REFERENCES

[1] Pestka, S., Langer, J.A., Zoon, K.C. and Samuel, C.E. (1987) Annu. Rev. Biochem. 56, 727–777.
[2] Mogensen, K.E., Uzé, G. and Eid, P. (1989) Experientia 45, 500–508.
[3] Merlin, G., Falcoff, E. and Aguet, M. (1985) J. Gen. Virol. 66, 1149–1152.
[4] Uzé, G., Lutfalla, G. and Gresser, I. (1990) Cell 60, 225–234.
[5] Aguet, M., Dembic, Z. and Merlin, G. (1988) Cell 55, 272–280.
[6] Hemmi, S., Peghini, P., Metzler, M., Merlin, G., Dembic, Z. and Aguet, M. (1989) Proc. Natl. Acad. Sci. USA 86, 9901–9905.
[7] Gaboriaud, C., Bissery, V., Benchetrit, T. and Mornon, J.-P. (1987) FEBS Lett. 224, 149–155.
[8] Bazan, F. (1990) Cell (in press).
[9] DeGrado, W.F., Wasserman, Z.R. and Chowhdry, V. (1982) Nature 300, 379–381.
[10] Denesyuk, A.I. and Zav'yalov, V.P. (1982) Immunol. Lett. 5, 223–226.
[11] Rehberg, E., Kelder, B., Hoal, E.G. and Pestka, S. (1982) J. Biol. Chem. 257, 11497–11502.