Marker Proteins in Inflammation

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Editors
P. Arnaud · J. Bienvenu · P. Laurent

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PREFACE

In the last week in June 1983, more than 250 research scientists and clinicians met at the Faculté Alexis Carrel, a School of Medicine (University, Claude Bernard, Lyon-I) located in Lyon, France. The participants had come from fifteen countries to participate in the "Second Symposium sur les Marqueurs de l'Inflammation" under the sponsorship of the "Groupe d'Etude et de Recherche sur les Marqueurs de l'Inflammation" (GERMI). The topics for this second symposium had been chosen by the International Scientific Committee of GERMI in order to provide a comprehensive view of the different aspects of the wide field of Marker Proteins in Inflammation and their clinical implications.

The proceedings begins with a series of papers concerning the mechanism of Acute Phase Reactant Proteins synthesis and the roles such proteins play in host defenses, a subject of perennial interest which was the main theme running throughout the meeting. The next three sections are devoted respectively to the protease anti-protease interplay in lung diseases, the importance of Acute Phase Proteins measurement in biological fluids for the diagnosis of joint diseases, and diseases of the central nervous system. The fourth section of the book deals with the role of zinc, protein deprivation, and malnutrition in host defenses. The fifth section features a group of papers on animal models of inflammation. Finally, the last section of the book reports on conferences held during a satellite lectins workshop arranged by Drs. Michel Caron et Alain Faure, which was devoted to three complementary aspects of lectins: their use as a tool for the study of glycoconjugates, their biological functions, and their affinity and specificity.

We wish to express our deepest gratitude to Professor Frank W. Putnam of the department of Molecular Biology and Biochemistry, Indiana University (Bloomington, Indiana, USA) who was the outstanding president

of this Symposium. We also want to extend our thanks to Professor Henry Gewurz, department of Immunology/Microbiology, Rush Medical College (Chicago, USA), Professor Robert Engler, department of Biochemistry, UER des Saints Pères (Paris, France) and Professor Roger Creyssel, department of Biochemistry UER Grange Blanche (Lyon, France), who acted as Symposium Co-Presidents and whose knowledge and understanding in the field made the program and its conferences possible.

We wish to thank the members of the Organizing Committee for their support and help. This includes Helene Bernon, Jacques Bienvenu, Philippe Laurent, Abel Roullet, and J.L. Touraine. The following institutions provided financial and practical support: GERMI, Institut Pasteur de Lyon et du Sud Est, Fondation Merieux, Société Française d'Immunologie, Association des Anciens Internes et Internes en Pharmacie de Lyon, Commission Médicale Consultative de Hospices Civils de Lyon, BioMerieux, Travenol France, Du Pont de Nemours, Hoechst-Behring, Boehringer Mannheim, Technicon, Roger Bellon. We would also like to express our sincere gratitude to Professor Maurice Carraz, Director of the Pasteur Institute of Lyon for his important help, and Dr. Charles Merieux, who hosted the International Scientific Advisory Committee of GERMI and organized the social events. We would like to express our thanks to all other individuals, companies and institutions who contributed to the success of the symposium.

The fact that expert researchers agreed to write papers on this rather new and important subject has made our job a considerable pleasure. We also extend our gratitude to the staff of Walter de Gruyter, Berlin, whose labors have led to the rapid publication of this second volume on Marker Proteins in Inflammation.

February 1984

P. Arnaud
J. Bienvenu
P. Laurent

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ELASTASE-α_1PROTEINASE INHIBITOR COMPLEX (E-α_1PI) AND C-REACTIVE PROTEIN (CRP): EARLY INDICATORS OF INFLAMMATORY PROCESSES.

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Introduction

In the course of inflammatory processes stimulation of phagocytosis and production of acute phase reactants are closely connected. Whereas acute phase proteins are synthesized as regulators of the inflammatory response d e n o v o by the liver cells, lysosomal enzymes of phagocytes are p r e f o r m e d and can be released immediately into the circulation during frustrated phagocytosis or cell disintegration. In this way, especially lysosomal proteinases from PMN granulocytes like elastase (E) may cause destructive processes before they are inactivated by plasma proteinase inhibitors, e.g. α_1-proteinase inhibitor (α_1PI). Increased levels of the E-α_1PI complex should be, therefore, a clear indication of the involvement of lysosomal proteinases in the inflammatory response (1).

Material and Methods

Using a recently developed enzyme-linked immunoassay (2) we determined the plasma levels of E-α_1PI in 41 patients subjected to major abdominal surgery as well as in 27 patients suffering from multiple trauma. The acute phase reactants C-reactive protein (CRP), α_1-antichymotrypsin (α_1AC) and C1-inactivator (C1 INA) were evaluated by radial immunodiffusion (LC- or M-Partigen, Behringwerke Marburg, FRG); α_1-proteinase inhibitor

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(α_1PI) and α_2-plasmin inhibitor (α_2PI) were measured by their inhibitory action on the target enzyme using chromogenic peptide substrates (Chromozym Try, Boehringer Mannheim FRG and S-2251, Kabi Stockholm, Sweden, respectively).

Results and Discussion

Septicemia

Thirty of 41 patients subjected to major abdominal surgery suffered from septicemia during the postoperative phase. Of these patients 14 survived the infection (group B) whereas the other 16 died as a direct result of septicemia (group C). The 11 patients without postoperative infection served as controls (group A).

Abdominal surgery (Fig. 1) was followed by an increase of E-α_1PI up to 3-fold of the mean standard value (60 to 110 ng/ml). Patients suffering from preoperative infections (6 out of 16 in group C), showed already significantly elevated preoperative E-α_1PI levels. Immediately after surgery, a slight decrease was observed, probably due to elimination of the infection focus. Before onset of sepsis, the E-α_1PI concentrations of groups B and C showed a moderate elevation but no significant changes compared to the early postoperative levels. However, at the beginning of septicemia a highly significant increase of the E-α_1PI levels could be detected, up to 6-fold in group B and up to 10-fold in group C. Peak levels were found to be higher than 2 500 ng/ml in both groups. The E-α_1PI levels of septic patients who recovered showed a clear tendency towards normal values. In patients with persisting septicemia, high levels of E-α_1PI were measured until death.

Daily measurements of pre- and early postoperative values of CRP and E-α_1PI in the control and septicemia groups designed both factors as being similarly sensible to the inflammatory stimulus (Fig. 1). In contrast to the E-α_1PI levels, however, the CRP levels did not allow discrimination of the severity of

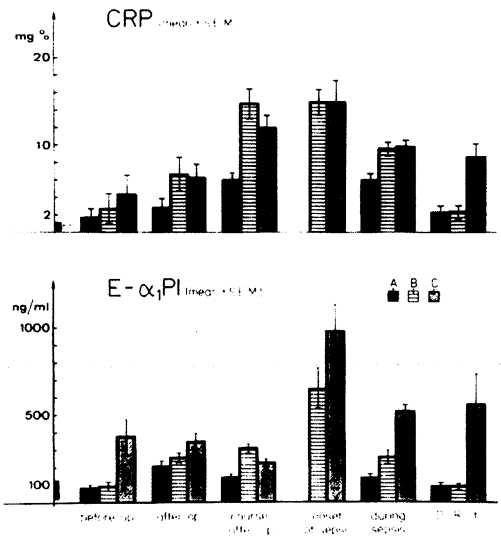

Fig. 1. Plasma levels of E-α_1PI complex and CRP in patients with major abdominal surgery.
A = without pop. I.
B = survival of pop. I.
C = death due to pop. I.
(pop. I. = postoperative infection).
Data are given as mean values for the day before operation, the day after operation, the period before onset of sepsis and the course of septicemia. The last determinations were done on the days of discharge (D) in group A, recovery (R) in group B, and before death (†) in group C. Normal range (nr) of E-α_1PI: 60-110 ng/ml.

the infection in the later postoperative phase, neither at onset nor during septicemia in both infected groups; only the last values were in agreement with clinical observations. Obviously, liberation of lysosomal elastase, probably due to an enhanced action of endotoxins on granulocytes throughout septicemia, does reflect more specifically this severe infection compared to CRP, which is supposed to play a central role in unspecific host defence (3).

Moreover, the plasma proteinase inhibitors (α_1AC, C1 INA, α_1PI and α_2PI) representing acute phase proteins did also not reflect the morbid state, likely due to an overlap of production and consumption of these glycoproteins (data not shown).

Multiple trauma

In a preliminary study release of granulocytic elastase into plasma was followed up every 4 hours in patients who suffered from multiple trauma. The increase of the E-α_1PI complex up to 16 hours after accident coincided clearly with the severity of the injury (Fig. 2), the degree of injury being established on the basis of a hospital internal scale ranging from 1-20 points. Group I patients (5 to 7 points) showed a maximal increase of E-α_1PI up to 5-fold above normal values and group II patients (9 to 11 points) up to 10-fold. In group III (14 to 17 points) peak levels higher than 20-fold above normal were measured. During the further observation period (up to 100 h) a significant decrease of E-α_1PI plasma levels towards normal values was observed in all patients.

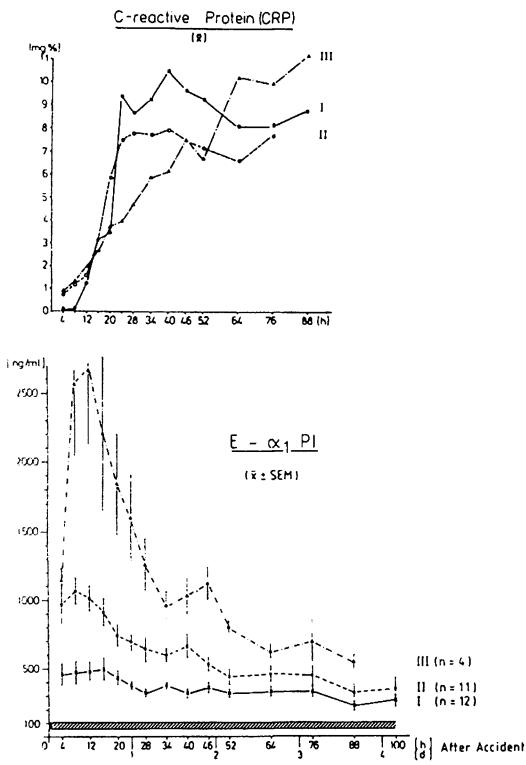

Fig. 2. Plasma levels of E-α_1PI complex and CRP in patients after multiple trauma. On the basis of a hospital internal scale with 20 points (HISP) patients were allied to 3 groups reflecting the severity of injury: I mild ; II severe; III highly severe.

Group	No. of patients	HISP
I	12	6.3±0.6
II	11	10.0±1.0
III	4	15.3±1.9

Normal range of E-α_1PI: 60 - 110 ng/ml

Maximal increase of CRP levels was observed normally between 20 and 40 h after accident (group I and II in Fig. 2). In a few cases (group III) maximal CRP values were measured up to 88 h after trauma (Fig. 2). Within the observation period, the CRP levels showed neither a statistically significant correlation to the severity of the injuries nor a clear tendency towards normalization. The same holds true for the plasma proteinase inhibitors responding as acute phase proteins (data not shown). In contrast to results published recently (4), we could so far not find a relationship between the amount of CRP in plasma and posttraumatic complications after cranio-cerebral injuries.

Conclusions

Although of all known acute phase proteins CRP rises most dramatically and rapidly, the given data demonstrate that complexed elastase (E-α_1PI) reflects the severity of an inflammatory response clearly earlier and more specifically. Hence, compared to lysosomal elastase increased production of acute phase proteins, at least of CRP, represents a delayed and less specific answer of the organisms to the primary inflammatory stimuli during diseases such as septicemia and multiple trauma.

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