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Mini-Review

High-Abundance Polypeptides of the Human Plasma Proteome Comprising the Top 4 Logs of Polypeptide Abundance

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BACKGROUND: Plasma contains thousands of proteins, but a small number of these proteins comprise the majority of protein molecules and mass.

CONTENT: We surveyed proteomic studies to identify candidates for high-abundance polypeptide chains. We searched the literature for information on the plasma concentrations of the most abundant components in healthy adults and for the molecular mass of the mature polypeptide chains in plasma. Because proteomic studies usually dissociate proteins into polypeptide chains or detect short peptide segments of proteins, we summarized data on individual peptide chains for proteins containing multiple subunits or polypeptides. We collected data on about 150 of the most abundant polypeptides in plasma. The abundant polypeptides span approximately the top 4 logs of concentration in plasma, from 650 to 0.06 μmol/L on a molar basis or from about 50 000 to 1 mg/L mass abundance.

CONCLUSIONS: Data on the concentrations of the high-abundance peptide chains in plasma assist in understanding the composition of plasma and potential approaches for clinical laboratory or proteomic analysis of plasma proteins. Development of more extensive databases regarding the plasma concentrations of proteins in health and diseases would promote diagnostic and proteomic advances.

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THE ABUNDANCE OF COMPONENTS OF THE PLASMA PROTEOME

Recent applications of diverse proteomic methods have enabled the detection of >3000 different protein components in plasma, with high-confidence identification of about one-third of the components *(1)*. The identification of individual components in plasma represents only a first stage in proteomic analysis, however. Quantitative analysis of components represents an important next step. Determination of the relative or absolute concentration of individual components in many plasma specimens usually represents a key step toward understanding the physiological significance or diagnostic potential of individual proteins. Quantitative analysis of the many components in the plasma proteome represents a major challenge, because the concentrations of different proteins extend over 12 orders of magnitude *(2, 3)*. There are a small number of proteins with very high abundance and a gradually increasing number of proteins at lower abundance. A single protein, albumin, represents more than half of the protein mass, and the dozen most abundant proteins usually comprise >95% of the total protein mass. The small number of high-abundance components tends to dominate most forms of proteomic analysis and limit the ability to detect low-abundance components. Selective depletion of a dozen high-abundance proteins extends analyses down about 1–2 orders of magnitude on the abundance scale *(4–11)*. This approach has extended the depth of proteome analysis, although it presents challenges in unintended losses of minor components and issues of reproducibility *(8–11)*. The present survey of high-abundance proteins suggests that depletion of about 150 major polypeptides extends the range of analysis to about 10 000-fold lower concentrations. A number of the high-abundance polypeptides are components of multichain proteins, so the total number of proteins requiring depletion is smaller than the number of polypeptides.

Although many efforts at proteomic analysis have considered high-abundance proteins to be a hindrance in the search for more interesting minor components, the high-abundance proteins represent many physiologically important molecules, such as immunoglobulins, apolipoproteins, protease inhibitors, coagulation factors, complement factors, and carrier molecules *(2, 12–14)*. Quantitative analysis of many of these high-abundance components is diagnostically useful for assessing nutrition, immune status, disorders of coagulation or fibrinolysis, disorders of lipoproteins, and acute-phase responses to injury or disease. Therefore,

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measurement of these molecules is an important part of clinical chemistry practice.

Because of their physiological and diagnostic significance as well as their impact on proteomic analysis, we sought to identify the concentrations of the most abundant plasma polypeptides and develop an approximate ranking of these components. This survey provides a ranking of the abundance of individual polypeptides on the basis of either molar concentration (Table 1) or mass abundance (Supplementary Table 1, which accompanies the online version of this article at http://www.clinchem.org/content/vol54/issue10). Ranking of the concentrations of polypeptide chains rather than of intact proteins offers a more representative measure for quantitative mass spectrometric methods that analyze dissociated polypeptide chains or small peptide fragments of proteins *(15–18)*.

APPROACH FOR IDENTIFYING HIGH-ABUNDANCE PLASMA PROTEINS

Decades of efforts at fractionation of plasma protein components and application of tools of protein chemistry identified more than 50 high-abundance protein components as summarized by Putnam in 1975 *(12)* and Peters in 1983 *(13)* and provided information about the structure of molecular forms in the circulation. We surveyed more recent studies using 2-dimensional electrophoresis for major components and bottom-up proteomic studies for frequently identified components *(19–26)*, and we examined studies that determined the concentrations of multiple plasma protein components *(27, 28)*. We searched data on human plasma proteins in the Peptide Atlas (http://www.peptideatlas.org) of the Institute for Systems Biology for polypeptides, with >20 identifications of tryptic peptides. We conducted literature surveys using MedLine and Google to identify information on the concentration and structure of the circulating forms of plasma proteins, and we surveyed textbooks for summary information on coagulation and complement components. We also surveyed reference intervals for clinical assays of proteins to identify components of high abundance and the reference intervals for these components. Sources of data are summarized in Supplementary Table 2 in the online Data Supplement. Ranking of components was according to the mean of their concentration range for healthy adults, where a range was identified. In some cases, where the distribution of concentrations has unusual distributions in the population, ranking by the median concentration or geometric mean might be preferable, but was not done in the present survey, because many references do not provide detailed information about the median or distribution of values in the population.

We obtained structural information from sequence databases and references describing protein analyses to identify the mass of the molecular forms of polypeptides that occur in the circulation rather than a calculated mass that does not account for the post-translational modifications of many of the proteins. Polypeptide masses determined by mass spectrometry are listed where this information was available *(29, 30)*.

RANKING OF THE MOST ABUNDANT POLYPEPTIDES IN PLASMA

An approximate ranking of the molar abundance of plasma polypeptides in healthy adults is provided in Table 1. This ranking should be most applicable for analytical approaches that respond to the number of molecules. Examples of such techniques are most immunoassay and mass spectrometric methods, where the signal response is related to the number of molecules rather than the size of molecules *(30)*. One approach for quantification of proteins that is seeing increased application is the analysis of tryptic peptides by liquid chromatography-triple quadrupole mass spectrometers with the use of stable isotope-labeled internal standards *(15–17)*. That technique determines the absolute concentration of one or more short peptide segments of a protein.

Ranking of polypeptides according to mass abundance (Supplementary Table 1 in the online Data Supplement) is more suitable to analytical approaches such as electrophoretic analysis with staining of polypeptides or ultraviolet detection of components resolved by electrophoresis or chromatography. High-molecular-weight components move up in this form of ranking and are more strongly represented in approaches using detection related to mass abundance rather than methods responding to the number of molecules.

The most appropriate ranking of the molecular forms of polypeptides and whether by molar concentration or mass abundance depends on the state of proteins in the method of analysis and the method of detection. A previous, more limited survey *(30)* provided a ranking of the molar abundance of covalently-bound polypeptide complexes, which would differ from the present ranking for proteins containing multiple disulfide-linked chains, such as immunoglobulins. That ranking of proteins was directed at analysis of proteins by MALDI-TOF mass spectrometry, which does not dissociate disulfide-linked polypeptides. One needs to consider whether proteins are analyzed under denaturing or reducing conditions.

DEVELOPING DATABASES OF POLYPEPTIDE AND PROTEIN CONCENTRATIONS

Two of the most important parameters in the analysis of plasma protein components are the sequences of individual components and their concentrations. Accu-

Table 1. Approximate molar abundance and masses of polypeptides in plasma from healthy subjects, based on literature survey.

Rank	Polypeptide	Concentration μmol/L	M_r
1	Albumin	500–800	66 400
2	Immunoglobulin κ, light chain	68–150	23 000
3	Immunoglobulin γ1, heavy chain	40–130	52 000
4	Immunoglobulin λ, light chain	36–84	23 000
5	Immunoglobulin γ2, heavy chain	20–90	52 000
6	Apolipoprotein A-I	30–70	28 100
7	Apolipoprotein A-II	30–60	8700
8	Transferrin	25–45	79 000
9	α_1-Antitrypsin	18–40	50 000
10	Immunoglobulin α1, heavy chain	8–50	57 000
11	Haptoglobin β-chain	6–40	35 000
12	Transthyretin subunit	15–30	13 800
13	Haptoglobin, α1-chain	0–40	9200
14	Haptoglobin, α2-chain	0–40	15 900
15	α_2HS-glycoprotein, heavy chain	9–30	38 400
16	α_2HS-glycoprotein, light chain	9–30	4000
17	Fibrinogen, α-chain	10–27	67 600
18	Fibrinogen, β-chain	10–27	52 300
19	Fibrinogen, γ-chain	9–24	49 000
20	Hemopexin	9–20	57 000
21	α_1-Acid glycoprotein, gene 1	9–20	40 000
22	Immunoglobulin μ, heavy chain	4–25	70 000
23	Apolipoprotein C-III	6–20	9000
24	α_2-Macroglobulin subunit	7–17	180 000
25	Gc-Globulin	8–14	51 000
26	Immunoglobulin γ3, heavy chain	2–16	50 000
27	Apolipoprotein C-I	6–12	6631
28	C3, α-chain	5–10	110 000
29	C3, β-chain	5–10	75 000
30	α_1-Acid glycoprotein, gene 2	4–10	40 000
31	Immunoglobulin γ4, heavy chain	0.3–13	50 000
32	α_1-Antichymotrypsin	4–9	68 000
33	Apolipoprotein D	2–10	23 000
34	β_2-Glycoprotein I	3–6	40 000
35	C4b–binding protein, α-chain	3–6	75 000
36	Apolipoprotein A-IV	3–6	43 000
37	Apolipoprotein C-II	2–7	8900
38	Serum amyloid A4	4	13 000
39	Bikunin chain, inter-α-trypsin inhibitor	3–5	30 000
40	Immunoglobulin α2, heavy chain	1–7	55 000
41	Antithrombin III	3–5	65 000
42	α_1B-Glycoprotein	3–5	63 000

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Table 1. Approximate molar abundance and masses of polypeptides in plasma from healthy subjects, based on literature survey. *(Continued from page 1610)*

Rank	Polypeptide	Concentration μmol/L	M_r
43	Gelsolin	3–5	80 000
44	Ceruloplasmin	2–5	135 000
45	Factor H	2–5	155 000
46	Factor B	2–5	100 000
47	Inter-α-trypsin inhibitor, heavy chain 1	2–4	65 000
48	Inter-α-trypsin inhibitor, heavy chain 2	2–4	70 000
49	Plasminogen	2–4	90 000
50	Kininogen, heavy chain	3	60 000
51	C1 Inhibitor	2–4	105 000
52	Low–molecular-weight kininogen, light chain	3	4000
53	α_1-Microglobulin	3	27 000
54	Retinol-binding protein	2–3	21 000
55	C1q, A-chain	2–3	27 000
56	C1q, B-chain	2–3	25 000
57	C1q, C-chain	2–3	23 000
58	Immunoglobulin, J-chain	0.5–4	16 000
59	Hemoglobin, α-chain	0.3–4	15 100
60	Hemoglobin, β-chain	0.3–4	15 900
61	Histidine-rich glycoprotein	1–3	58 500
62	Apolipoprotein F	2	30 000
63	Paraoxonase	2	45 000
64	Apolipoprotein B-100	1–3	550 000
65	Vitronectin	1–3	75 000
66	Clusterin, α-chain	1–2	35 000
67	Clusterin, β-chain	1–2	37 000
68	Serum amyloid P	1–2	25 500
69	Afamin	1–2	75 000
70	Pre-α-inhibitor, heavy chain 3	1–2	90 000
71	Inter-α-trypsin inhibitor–related protein, heavy chain 4	1–2	120 000
72	Fibrinogen, γ′-chain	1–2	51 000
73	Prothrombin	1.5	72 000
74	Heparin cofactor II	1.5	65 600
75	Transcortin	1.4	53 000
76	High–molecular-weight kininogen, light chain	1.4	50 000
77	Apolipoprotein E	0.6–2	35 000
78	C4A and C4B, β-chain	0.5–2	78 000
79	C4A and C4B, γ-chain	0.5–2	33 000
80	Zinc α_2-glycoprotein	0.8–1.6	38 500
81	C1r	1	95 000
82	C1s	1	85 000
83	α_2-Antiplasmin	1	63 000
84	Angiotensinogen	1	65 000

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Table 1. Approximate molar abundance and masses of polypeptides in plasma from healthy subjects, based on literature survey. *(Continued from page 1611)*

Rank	Polypeptide	Concentration μmol/L	M_r
85	Fibronectin	1	275 000
86	Factor H–related protein 1	1	37 000
87	Haptoglobin-related protein, β-chain	0.6–1.2	35 000
88	Haptoglobin-related protein, α-chain	0.6–1.2	10 000
89	Glutathione peroxidase 3	0.8	23 000
90	C4b–binding protein, β-chain	0.5–1	45 000
91	C8, α-chain	0.5–1	64 000
92	C8, β-chain	0.5–1	64 000
93	C8, γ-chain	0.5–1	22 000
94	C7	0.5–1	120 000
95	C9	0.4–1	79 000
96	C6	0.5–0.9	95 000
97	Tetranectin subunit	0.4–0.9	20 000
98	C4A, α-chain	0.3–1	95 000
99	C4B, α-chain	0.3–1	95 000
100	Prekallikrein	0.6	86 000
101	Factor H–related protein splicing variant	0.2–1	49 000
102	Lysozyme	0.01–1	14 700
103	Factor I, heavy chain	0.5	50 000
104	Factor I, light chain	0.5	38 000
105	C5, α-chain	0.4–0.6	115 000
106	C5, β-chain	0.4–0.6	75 000
107	Fibulin-1	0.4–0.6	80.000
108	Immunoglobulin δ, heavy chain	0–1	65 000
109	Glycosylphosphatidylinositol-specific phospholipase D	0.2–0.8	120 000
110	Serum amyloid A	0–0.9	11 700
111	Ficolin-3 subunit	0.2–0.7	34 000
112	Leucine-rich α_2-glycoprotein	0.4	50 000
113	Properdin	0.4	55 000
114	Factor XII	0.3–0.5	80 000
115	Thyroxine-binding globulin	0.2–0.5	58 000
116	Protein S	0.3	69 000
117	Adiponectin subunit	0.3	28 000
118	Ficolin-2 subunit	0.03–0.4	35 000
119	C2	0.1–0.3	100 000
120	Kallistatin	0.2	58 000
121	Apolipoprotein L	0.2	42 000
122	Factor X, heavy chain	0.2	42 000
123	Factor X, light chain	0.2	16 000
124	Factor XIII, α-chain	0.2	75 000
125	Factor XIII, β-chain	0.2	80 000
126	Fibrinogen, αE-chain	0.1–0.3	95 000

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Table 1. Approximate molar abundance and masses of polypeptides in plasma from healthy subjects, based on literature survey. *(Continued from page 1612)*

Rank	Polypeptide	Concentration μmol/L	M_r
127	Apolipoprotein C-IV	0.07–0.3	14 000
128	Procarboxypeptidase	0.07–0.3	55 000
129	C-reactive protein	0.01–0.3	23 000
130	Hyaluronan-binding protein	0.07–0.2	75 000
131	Sex hormone–binding protein	0.03–0.2	45 000
132	β_2-Microglobulin	0.08–0.16	11 700
133	Factor D (adipsin)	0.04–0.2	24 400
134	Insulinlike growth factor–binding protein 3	0.07–0.17	42 000
135	Mannose-binding protein	0.1	24 000
136	Lipopolysaccharide-binding protein	0.1	60 000
137	Factor IX	0.1	57 000
138	Protein C, heavy chain	0.1	41 000
139	Protein C, light chain	0.1	21 000
140	Protein C inhibitor	0.1	53 000
141	Apolipoprotein M	0.1	26 000
142	Pigment epithelium–derived factor	0.1	46 500
143	S100 A9	0.05–0.14	13 200
144	S100 A8	0.05–0.14	10 700
145	Apolipoprotein(a)	0.002–0.15	variable
146	Factor XI	0.06–0.09	87 000
147	Apolipoprotein B-48	0.03–0.1	270 000
148	Cholinesterase	0.04–0.08	85 000
149	Cystatin C	0.04–0.08	13 000
150	von Willebrand factor subunits	0.04–0.08	240 000

rately assessing the concentration often represents the more challenging problem, as concentration may vary with many physiological, population, preanalytical, and analytical variables. Many years of experience in clinical chemistry laboratories show that establishing reference intervals for specific components can be a challenging task that can require widespread collaboration for standardization of analyses and the application of best available reference methods of analysis *(31)*. Experience with the analysis of apolipoproteins provides good examples of the method-dependent variation in results and challenges in establishing reference intervals *(32)*. For many of the entries in Table 1, available studies offer concentration data on only a small number of specimens, physiological characteristics of subjects providing the specimens may be incompletely identified, and methods used for analysis may be imprecise or lacking well-characterized standards for calibration. There clearly is a need for more extensive reference range data for many of the abundant polypeptides.

The method of specimen collection can have significant effects on the composition of components. In particular, there is considerable change in the composition of plasma when it is allowed to clot and to form serum. Some of the coagulation components (such as fibrinogen chains) are removed, activation peptides are generated, and platelet components are released *(30, 33, 34)*. Plasma specimens generally have been preferred for proteomic studies *(34)*. Many physiological and pathological processes also lead to major changes in the concentrations of multiple plasma proteins. The acute-phase response is a well-characterized example of a process dramatically affecting the concentrations of many components *(35)*. Thus, it becomes necessary to determine the changes in concentration of a protein for each physiological or pathological process of interest as well as the reference intervals for healthy subjects.

The issues noted above present challenges in developing a database of reference ranges for protein or polypeptide concentrations. This challenge must be

addressed routinely by clinical laboratories or vendors of in vitro diagnostic tests and for special populations such as pediatric patients *(36–38)*. To be of optimal utility, data on protein concentrations need to include information on the population, specimen types, analytical method, and distribution of results. Collection of more extensive data on the concentrations and structural variation of a wider range of plasma components would assist in providing a general frame of reference for plasma proteomic and diagnostic analysis.

The present effort to develop a listing of high-abundance polypeptides is admittedly a simplification. Some proteins undergo proteolytic processing that can yield internally cleaved or truncated forms, and there can be variation in posttranslational modification of proteins. Many of the posttranslational modifications of individual polypeptides are listed in Supplementary Table 2 in the online Data Supplement. Supplementary Table 2 also includes synonyms for protein names, links to sequence databases, and references for polypeptide abundance and mass. Some genes are duplicated, such as for α_1-acid glycoprotein (gene 1 and 2) and the fourth component of complement (C4A and C4B). The duplicated gene products are highly homologous and are differentiated by a limited number of sequence substitutions. Only a few of the many tryptic peptides from these proteins distinguish different gene products. Some of the related polypeptides such as apolipoprotein B-48 and B-100 and haptoglobin α1- and α2-chains are more likely to be distinguished by top-down analysis of intact polypeptides than by bottom-up analysis of tryptic peptides. Immunoglobulin chains represent a set of millions of different sequences, with sequence variation of the variable domains and defined sequences for the constant domains. Therefore, the listed molar concentrations of immunoglobulin chains apply only to the constant domains and not to the complete polypeptide chains. From 2-dimensional electrophoresis, there is evidence for increased clonal expression of a few hundred light-chain molecules, which therefore achieve a concentration approximately in the 0.1–1 μmol/L range *(2)*. It has not been determined whether there are similar subsets of heavy-chain clones with increased expression.

The present list offers representation of only a few examples of alternatively spliced forms of proteins. Fibronectin, for example, is known to occur in multiple spliced forms *(39)*, but these were not broken out as separate entries for the present list. Advances in our understanding of the plasma proteome should allow progressive improvement in the delineation of major structural variants of proteins and their concentrations.

The list of high-abundance components in Table 1 and Supplementary Table 1 in the online Data Supplement should be viewed as a work in progress. As additional quantitative data about the abundance of plasma polypeptides becomes available, the ranking of some components will change and additional polypeptides within the high-abundance range will be added. The Peptide Atlas, which identifies tryptic peptides derived from thousands of polypeptides in human plasma, represents a database that might be further explored for candidates for high-abundance polypeptides. Our preliminary search of the Peptide Atlas identified a number of additional proteins with relatively frequent peptide identifications for which independent measures of protein concentration by immunoassay or other techniques were not found. Those results suggest that there will be further additions to the roster of high-abundance polypeptides.

THE SIGNIFICANCE OF HIGH-ABUNDANCE PLASMA POLYPEPTIDES

The high-abundance polypeptides in Table 1 predominantly represent major secretory proteins released from abundant tissues such as liver, lymphoid and hematopoietic tissues, and intestines. A few other tissues are rarely represented, such as adipose tissue by adipsin and endothelial cells by von Willebrand factor. Intracellular proteins are represented by only a few examples such as hemoglobin chains. There is limited representation of products from other major tissues such as epidermis, bone, muscle, lung, pancreas, kidneys, and central nervous system, or of small specialized organs such as prostate, ovary, thyroid, and pituitary. Efforts such as the Human Protein Atlas *(40)* might help clarify the sources of high-abundance proteins and identify additional candidates from major organs that have limited representation in the current list of high-abundance proteins.

The high-abundance polypeptide components, although critical to systemic physiology, appear to represent primarily products of a few major tissues. Therefore, the search for polypeptides that can serve as diagnostic markers for disorders of other tissues or of small early-stage tumors may be justified in an interest in low-abundance components. The only changes detected among high-abundance components in such disorders of many tissues may be nonspecific responses to injury.

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