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Natural autoantibodies in healthy neonatals recognizing a peptide derived from the second conserved region of HIV-1 gp120

Prirodna antitela prisutna kod zdrave novorođenčadi koja prepoznaju peptid poreklom iz drugog konzerviranog regiona HIV-1 gp120

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Abstract

Background/Aim. High sera reactivity with a peptide derived from human immunodeficiency virus HIV-1 envelope protein gp120, NTM1, correlate with non-progressive HIV-1 infection and also may have protective role in breast and prostate cancer. We also detected a low NTM1 reactive antibodies titer in healthy HIV negative sera and showed that antibody levels can be significantly increased with vigorous physical activity. However, the immune system seems to be unresponsive or tolerant to this peptide, implicating that the NTM1 sequence encompasses or overlaps a certain innate immune epitope. The aim of this study was to present evidences that NTM1 – binding antibodies – are components of innate immune humoral response, by confirming their presence in sera of newborn babies. For this purpose we collected a set of 225 innate antigen sequences reported in the literature and screened it for candidate antigens with the highest sequence and spectral similarity to NTM1 derived from HIV-1 gp120. **Methods.** Sera from 18 newborns were tested using ELISA, with peptide NTM1. Sequences from innate antigen database were aligned by an EMBOSS Water bioinformatics tool. **Results.** We identified NTM1 reactive antibodies in sera of HIV negative newborn babies. Further, in order to identify which of already known innate antigens are the most similar to NTM1 peptide we screened innate immune antigen sequence database collected from the literature. This screening revealed that the most similar sequence are ribonucleoproteins RO60, in addition to previously identified N-terminus of vasoactive intestinal peptide. **Conclusion**. The results of this study confirm the hypothesis that NTM1 recognizing antibodies are a part of humoral innate immune response. Further, computational similarity screening revealed a vasoactive intestinal peptide and RO60 as the most similar sequences and the strongest candidate antigens. In the light of the presented results, it is appealing that testing blood reactivity at birth, with specific innate antigens, particularly a vasoactive intestinal peptide, can reveal the potential to develop or boost protective immune response in breast and prostate cancer and HIV infection later in life.

Key words:
immunity, innate; infant, newborn; infant, premature; antibodies; vasoactive intestinal peptide; hiv envelope protein gp120.

Apstrakt

Uvod/Cilj. Visoka reaktivnost seruma na peptid NTM1, poreklom iz proteina omotača gp120 virusa humane imunodeficijencije, HIV-1, koreliše sa neprogresivnom HIV-1 infekcijom, a, takođe, može imati zaštitnu ulogu u kanceru dojke i prostate. Nedavno smo detektovali nizak titar antitela reaktivnih na NTM1 i u zdravim HIV-negativnim serumima i pokazali smo da se nivo ovih antitela može značajno povećati energičnom fizičkom aktivnošću. Međutim, postoje dokazi da je ovaj peptid neimunogen ili da je nevidljiv za imuni sistem čoveka, čime se sugeriše da NTM1 sekvenca obuhvata ili se preklapa sa određenim epitopom urođene imunosti. Cilj ove studije bio je da se dokumentuje da su vezivna antitela, NTMI, sastavni delovi urođenog humoralnog imunog odgovora potvđivanjem njihovog prisustva u serumu novorođenčadi. U tu svrhu, sakupili smo ukupno 225 urođenih sekvenci antigena prikazanih u literaturi i testirali ih za kandidate antigena sa najvećom sličnošću sekvence i spektra NTM1 nastalih iz HIV-1 gp120. **Metode.** Serumi 18 novorođenčadi testirani su ELISA probama sa NTM1 peptidom vezanim za ploču. Poravnavanje sekvenci urođenih antigena vršeno je bioinformatičkim alatom EMBOSS Water. **Rezultati.** U serumima HIV negativnih novorođenčadi identifikovali smo antitela reaktivna na NTM1. Dalje, da bi utvrdili koji od već poznatih antigena urođene imunosti je najsličniji peptidu NTM1, pretražili smo bazu sekvenci antigena urođene imunosti formirane na osnovu literaturih

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podataka. Ovo pretraživanje pokazalo je da, pored predhodno identifikovanog N-terminusa vazoaktivnog intestinalnog peptida, najsličnija je NTM1 peptidu sekvenca ribonukleoproteina RO60. **Zaključak.** Ovom studijom potvrdili smo hipotezu da su antitela koja prepoznaju NTM1 deo urođenog humoralnog imunog odgovora. Dalje, kompjuterskim pretraživanjem sličnosti utvrdili smo da su vazoaktivni intestinalni peptid i RO60 sekvence najsličnije NTM1 i, tako, najjači kandidati za antigene. U svetlu predstavljenih rezultata, privlačna je ideja da testiranje reaktivnosti krvi sa specifičnim urođenim antigenima, pre svega vazoaktivnim intestinalnim peptidom na rođenju, može otkriti potencijal za razvoj protektivnog imunog odgovora kasnije u životu i to ne samo za određene autoimune bolesti, već i za kancer dojke i prostate, kao i HIV infekcije.

Ključne reči:
imunitet, prirodni; novorođenče; novorođenče, prevremeno; antitela; vazoaktivni intestinalni peptid; protein omotača gp120 virusa hiv.

Introduction

In spite tremendous progress that has been made by introducing highly active antiretroviral therapy (HAART) in inhibiting HIV-1 virus through disrupting reverse transcription, integration or proteolytic processing of viral proteins, some important problems as persistent viral reservoirs, drug resistance and toxicities still remain. HAART can effectively keep the viral replication at an undetectable level, prolonging the life expectancy of the infected and reducing the viral transmission. However, several host and virus factors can slow down and block the disease progression [1–4] and also, various immunological factors [5, 6] might play an important role. NTM1 peptide, derived from the C-terminus of the second conserved region of HIV-1 envelope protein gp120, and anti-NTM1 antibodies have been suggested to be important in controlling HIV disease. These antibodies have been significantly prevalent in sera of long-term nonprogressors (LTNP), the HIV positives that are capable of keeping viral load bellow 10 000 copies/mL without any retroviral therapy for more than 10 years. The same is observed in patients in asymptomatic phase of the HIV-1 disease [7]. NTM1 binding antibodies are reported in a small number of healthy individuals and extremely high titer values are detected in elite athletes [8]. Although the immune system seems to be unresponsive or tolerant to this peptide [9–11], the titer NTM1 recognizing antibodies can be increased by continuous and vigorous exercising [12]. Taken together these data implicate that NTM1 peptide encompasses or overlaps the innate immune epitope sequence involved in cellular pathway activated by physical activity. Based on the sequence similarity and *in vitro* cross-reactivity we previously hypothesized that the candidate binding antigen for these was vasoactive intestinal peptide (VIP), the pleiotropic extracellular molecule important in many physiologic functions, including glucose homeostasis, neuroprotection, memory, gut function, modulation of the immune system and circadian function. Due to its important immunomodulatory and neuromodulatory activities, circulating levels of VIP are under tight control. Natural anti-VIP autoantibodies are potent modifiers of its biological actions and important regulators of its circulating level [13–17].

Natural autoantibodies (NAbs) are an important component of the immune system, existing in all vertebrates and demonstrating a non-pathogenic anti-self reactivity [18]. NAbs are reactive with only a restricted and specific set of proteins [19]. The function of these antibodies, although not fully elucidated, is to provide early innate immune protection against certain pathogens, as well as the removal of possible autoantigens through scavenging dead or apoptotic cellular debris through the lifetime (for review see Lutz et al. [20]). In general, mediators of innate humoral immunity are low-affinity polyreactive antibodies with an ability to bind to diverse, similar epitopes.

The aim of this study was to present evidences that NTM1-binding antibodies are components of innate immune humoral response, by confirming their presence in sera of newborn babies. For this purpose we collected a set of 225 innate antigen sequences reported in the literature and screened it for candidate antigens with the highest sequence and spectral similarity to NTM1 derived from HIV-1 gp120. Computational similarity screening revealed VIP and a ribonucleoprotein, RO60, as the most similar sequences and the strongest candidate antigens, although other highly similar sequences were also identified. These results imply that testing blood reactivity with specific innate antigens at birth can reveal potential to develop or boost protective immune response in breast and prostate cancer and HIV infection.

Methods

Sequences

The HIV1 gp120 NTM1 sequence was as in paper of Djordjevic et al. [21] Innate immune antigen sequences are listed in Addendum 1.

Sequence alignments

Sequence alignments are calculated by an EMBOSS Water, a tool that uses the Smith-Waterman algorithm to calculate the local alignment of two sequences [22]. Sequences with scores higher than 20 (scores were from 7 to 23) are selected as candidate antigens.

Human subjects

Sera were collected from 9 preterm and 9 term newborns within the first 7 days after birth. The preterm infants were born between the weeks 27–34 of gestation, with the weight 950–2,200 g. The term newborns were born after 37 weeks of gestation, with the weight more than 2,500 g. After centrifugation, sera were collected and stored at -20°C. The sample material used in this study was what remained of serum used for standard biochemical testing. Blood specimens were not collected specifically for these experiments. The study was approved by the Ethics Committee of the Institute for Neonatology, Belgrade, Republic of Serbia.

ELISA

ELISA was performed with peptide (NTM1)4-SOC4 by the following procedure: polystyrene microtiter plates (Greiner, Germany) were incubated overnight at 4°C with 100 µl of peptides (1.25 µg/well) diluted in carbonate buffer, pH 9.6. Plates were washed with phosphate-buffered saline (PBS)–0.05% Tween and non-specific sites were blocked with 200 µl PBS containing 5% bovine serum albumin (BSA) for 2 h at room temperature. After 6 washings, serum specimens were added to the wells (100 µl /well). Sera were diluted 1 : 20 in 5% BSA in PBS. Plates were incubated for 4h at room temperature. After 6 washings with PBS–0.05% Tween, 100 µl of goat anti-human IgM alkaline phosphatase-conjugated antibodies (Sigma), diluted 1 : 50 were added and the plates were incubated for 30 minutes at room temperature. After 6 washings, p-nitrophenyl phosphate (pNPP) substrate was added and the absorbance optical density (OD) measured at 405–620 nm after 15 minutes. Each sample was tested twice. As a control we used antigen from Serion ELISA classic Cytomegalovirus IgM (Institute Virion\Serion GmbH).

Statistical analysis

The significance of the differences in O.D. values for preterm and term infants was calculated by Student's *t*-test, as the sample sizes were relatively small. The 2 groups were unpaired with uneven variance and therefore they were considered as part of a two-tailed, heteroscedastic matrix.

Results

In order to show that NTM1 binding antibodies are innate natural self-binding antibodies we determined their presence in sera of HIV-1 negative neonates. Our previous studies showed the presence of NTM1 antibodies of IgG subclass in HIV positive LTNPs, as well as in elite athletes and in small percentage of healthy HIV- adult population [7, 23], but here NTM1 binding of IgM subclass of antibodies specific to neonatal population were measured. Maternal antibodies of IgG subclass actively transfer across the placenta and therefore can be related to her adaptive immune response [24]. Reactivity of sera in a small cohort of 18 HIV-1 negative new born babies (Table 1) was determined by the ELISA immunoassay (Figure 1). Statistical analysis revealed that this reactivity in sera from preterm neonates was significantly higher in comparison with the reactivity of term neonates ($p < 0.001$).

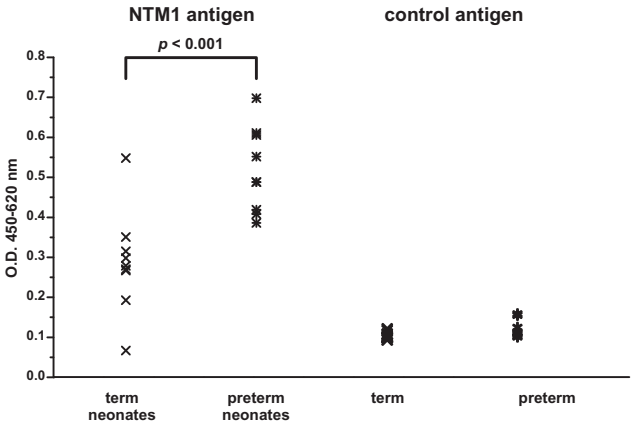

Fig. 1 – ELISA results of sera reactivity in the preterm and the term neonates. Antibodies recognizing peptide NTM1 were significantly more prevalent in serum samples from the preterm neonates compared to the term neonates ($p < 0.001$).

In search for innate epitopes similar to NTM1 we screened literature data and identified 225 protein sequences reported to encompass innate immune epitopes (Addendum 1) [20, 25–47]. Considering the ability of natural antibodies to bind to diverse epitopes we selected the set candidate antigens as described in Methods section (Table 2).

Discussion

Certain types of autoreactive immune cells and antibodies are common in healthy individuals and play an important role in body homeostasis. Several functions have been assigned to NAbs: neutralization of microbes and microbial toxins as natural first-line defence against infection, removal of senescent/altered self molecules and cells and immunomodulation and immunosignaling. New and unexpected insights into the functional roles of NAbs are still emerging, especially regarding their protective functions. NAbs are encoded by V(D)J genes in germline configuration and belong to IgG, IgM and IgA subclasses.

Several studies which investigated humoral immune response associated with the control of HIV-1 disease progression showed that the antibodies recognizing the peptide derived from C-terminus of the second conserved region of HIV-1 gp120, NTM1, correlate with non-progressive HIV-1 infection. Recently, the potential protective role of NTM1 antibodies has also been shown in breast and prostate cancer patients. Due to the fact that the peptide NTM1 is not immunogenic in

Table 1

Characteristics of infants at birth and the mean NTM1 ELISA absorbance values

Characteristics of infants	Preterm (n = 9)	Term (n = 9)
Gestational age at birth (weeks)	< 34	> 37
Birth weight (grams)	< 2500	> 2500
Sampling days	< 7	< 7
Absorbance values for NTM antigen, $\bar{x} \pm SD$	0.517 ± 0.107	0.287 ± 0.128
Absorbance values for control antigens, $\bar{x} \pm SD$	0.120 ± 0.022	0.106 ± 0.009

Table 2

Candidate antigens for NTM1 natural autoantibodies

Protein name	AC No	Score	Pairwise sequence alignment
VIP	P01282	23	NTM1 1 FTDN 4 |||| VIP_HUMAN 130 FTDN 133
RO60 ribonucleoprotein	P10155	23	NTM1 1 FTDN 4 |||| RO60-HUMAN 467 FTDN 470
ATP synthase subunit alpha	P25705	22	NTM1 1 FTDNAK 6 |.||.| ATPA_HUMAN 300 FRDNGK 305
Histone H2A 2C	Q16777	21	NTM1 3 DNAKT 7 ||.|| H2A2C_HUMAN 73 DNKKT 77
Serum albumin	P02768	21	NTM1 1 FTDNAKT 7 |.||.:| ALBU_HUMAN 151 FHDNEET 157
Hsp70	P08107	21	NTM1 1 FTDNAKTI 8 |||..:.| HSP71_HUMAN 44 FTDTERLI 51
Hsp71	P11142	21	NTM1 1 FTDNAKTI 8 |||..:.| HSP7C_HUMAN 44 FTDTERLI 51
Myeloperoxidase	P05164	21	NTM1 1 FTDNAKTI 8 |.||.:.: PERM_HUMAN 369 FQDNGRAL 376
Fibronectin	P02751	21	NTM1 1 FTDNAKT 7 ||.|.:| FINC_HUMAN 364 FTYNGRT 370
Thyroglobulin	P01266	21	NTM1 1 FTDNAKTI 8 ||.|.|.: THYG_HUMAN 460 FTTNPKRL 467

VIP – vasoactive intestinal peptide.

humans, it has been suggested that the antibodies recognizing this peptide represent natural autoantibodies. Thus, we have confirmed this hypothesis by detecting NTM1 antibodies in newborn babies. Sera samples of a small cohort of 18 newborns not older than 7 days tested in ELISA experiments showed a significant binding to NTM1 peptide. The difference between preterm and term serum titers are in line with already observed major differences of functional immune components between these two categories of neonates as reviewed in Sharma et al. [48]. This may be explained by specific innate immune defense pathways in protecting preterm infants against infection, or by deregulated innate immune responses which play a major role in the etiology of certain preterm neonatal complications later in life. Further, assuming that NTM1 recognizing antibodies belong to the majority of NAbs displaying rather low affinity and polyreactivity for a range of ligands [49] we scanned the set of innate antigen sequences in order to identify those that are most similar to NTM1. The collection of the 225 tested protein sequences from literature data represents significant, but far from exhaustive list of innate immune antigens (Addendum 1). Based on this inquiry we selected 10 most similar sequences as potential binding antigens for NTM1 recognizing antibodies (Table 2). The two prominent candidate antigens which show the highest similarity score to NTM1 are extracellular VIP, whose sera titer is tightly regulated by NAbs and RO60, which is an antigen for anti-RO60 antibodies involved in the clearance of apoptic debris [50]. These findings are in perfect agreement with major functional roles attributed to the natural IgM antibodies in the maintenance of tissue homeostasis and immune regulation [51–53]. However, we suggest that more probably VIP serves as the most important self-binding molecule for these antibodies for the following reasons: it was identified as one of the most important nodes in IgM antigen network conserved in both, mothers and babies [54], NTM recognizing IgG antibodies are cross-reactive with VIP in sera of HIV positives and in

healthy adults [55], and the levels of circulating VIP in newborns are significantly prevalent in preterm neonates compared to term born babies [56] which could explain the statistically significant prevalence of NTM1 recognizing antibodies ($p < 0.001$) in our study.

Conclusion

The information about the presence of NTM1 recognizing natural antibodies at birth may be of significant importance later in life due to the fact that these antibodies might have protective roles in HIV-1 disease and in breast or prostate cancer. Previous findings that these NAbs are retained throughout life with potential of sera titer to be significantly increased by physical exercise emphasize the need for future exploration of NTM1 recognizing antibodies as personalized therapeutic strategy based on the natural antibodies repertoire. In the light of the presented results, it is appealing that testing blood reactivity at birth, with specific innate antigens, particularly vasoactive intestinal pephole (VIP), can reveal the potential to develop or boost protective immune response against certain life threatening diseases.

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Addendum 1

Innate immune antigen sequences

Protein name	SwissProt ID	Reference
Alpha-2-macroglobulin precursor - Homo sapiens (Human)	[P01023]	24
Acetylcholinesterase precursor - Homo sapiens (Human)	[P22303]	24
Serum albumin precursor - Homo sapiens (Human)	[P02768]	24
Fructose-bisphosphate aldolase A - Homo sapiens (Human)	[P04075]	24
Fructose-bisphosphate aldolase B - Homo sapiens (Human)	[P05062]	24
Fructose-bisphosphate aldolase C - Homo sapiens (Human)	[P09972]	24
Amyloid beta A4 protein-Homo sapiens (Human)	[P05067]	25
Anion exchange protein 3-Homo sapiens (Human)	[P48751]	26
Atrial natriuretic factor precursor - Homo sapiens (Human)	[P01160]	24
Natriuretic peptides B precursor [Contains: Gamma-brain natriuretic peptide; Brain natriuretic peptide 32 - Homo sapiens (Human)	[P16860]	24
Annexin A10 - Homo sapiens (Human)	[Q9UJ72]	24
Annexin A11 - Homo sapiens (Human)	[P50995]	24
Annexin A13 - Homo sapiens (Human)	[P27216]	24
Annexin A1 - Homo sapiens (Human)	[P04083]	24
Annexin A2 - Homo sapiens (Human)	[P07355]	24
Annexin A3 - Homo sapiens (Human)	[P12429]	24
Annexin A4 - Homo sapiens (Human)	[P09525]	24
Annexin A5 - Homo sapiens (Human)	[P08758]	24
Annexin A6 - Homo sapiens (Human)	[P08133]	24
Annexin A7 - Homo sapiens (Human)	[P20073]	24
Annexin A8 - Homo sapiens (Human)	[P13928]	24
Annexin A9 - Homo sapiens (Human)	[O76027]	24
ATP synthase subunit alpha, mitochondrial-Homo sapiens (Human)	[P25705]	27
ATP synthase subunit beta, mitochondrial-Homo sapiens (Human)	[P06576]	27
Beta-2-glycoprotein 1 precursor - Homo sapiens (Human)	[P02749]	24
Beta-2-microglobulin precursor [Contains: Beta-2-microglobulin form pI 5.3] - Homo sapiens (Human)	[P61769]	24
Complement C1q subcomponent subunit A precursor - Homo sapiens (Human)	[P02745]	24
Complement C1q subcomponent subunit B precursor - Homo sapiens (Human)	[P02746]	24
Complement C1q subcomponent subunit C precursor - Homo sapiens (Human)	[P02747]	24
Calcitonin precursor [Contains: Calcitonin; Katacalcin - Homo sapiens (Human)	[P01258]	24
Caspase-3 precursor - Homo sapiens (Human)	[P42574]	24
Caspase-8 precursor - Homo sapiens (Human)	[Q14790]	24
Catalase - Homo sapiens (Human)	[P04040]	24
C-C chemokine receptor type 5- Homo sapiens (Human)	[P51681]	28, 29
C-X-C chemokine receptor type 4- Homo sapiens (Human)	[P61073]	28
Citrate synthase, mitochondrial- Homo sapiens (Human)	[O75390]	30
T-cell surface glycoprotein CD4- Homo sapiens (Human)	[P01730]	28, 31, 32
Cyclin-A1 - Homo sapiens (Human)	[P78396]	24
Cyclin-A2 - Homo sapiens (Human)	[P20248]	24
Choriogonadotropin subunit beta precursor - Homo sapiens (Human)	[P01233]	24
60 kDa heat shock protein, mitochondrial precursor - Homo sapiens (Human)	[P10809]	24
Coagulation factor VIII Homo sapiens (Human)	[P00451]	33, 34
Collagen alpha-1(I) chain precursor - Homo sapiens (Human)	[P02452]	24
Collagen alpha-2(I) chain precursor - Homo sapiens (Human)	[P08123]	24
Complement component C9 precursor [Contains: Complement component C9a; Complement component C9b] - Homo sapiens (Human)	[P02748]	24
Collagen alpha-1(X) chain precursor - Homo sapiens (Human)	[Q03692]	24
Corticotropin-lipotropin precursor - Homo sapiens (Human)	[P01189]	24
Corticoliberin precursor - Homo sapiens (Human)	[P06850]	24
C-reactive protein precursor [Contains: C-reactive protein(1-205)] - Homo sapiens (Human)	[P02741]	24
Cytotoxic T-lymphocyte protein 4 precursor - Homo sapiens (Human)	[P16410]	24
Glutamate decarboxylase 1 - Homo sapiens (Human)	[Q99259]	24
Glutamate decarboxylase 2 - Homo sapiens (Human)	[Q05329]	24
Granulocyte-macrophage colony-stimulating factor- Homo sapiens (Human)	[P04141]	35
DnaJ homolog subfamily B member 1 - Homo sapiens (Human)	[P25685]	24
Endoplasmin/ gp96 homolog- Homo sapiens (Human)	[P14625]	27
Endothelin-1 precursor - Homo sapiens (Human)	[P05305]	24
Endothelin-2 precursor - Homo sapiens (Human)	[P20800]	24
Alpha-enolase- Homo sapiens (Human)	[P06733]	27
Pro-epidermal growth factor precursor - Homo sapiens (Human)	[P01133]	24

Leukocyte elastase precursor - Homo sapiens (Human)	[P08246]	24
Coagulation factor X precursor - Homo sapiens (Human)	[P00742]	24
Coagulation factor VII precursor - Homo sapiens (Human)	[P08709]	24
Alpha-2-HS-glycoprotein precursor - Homo sapiens (Human)	[P02765]	24
Fetuin-B precursor - Homo sapiens (Human)	[Q9UGM5]	24
Fibrinogen alpha chain precursor [Contains: Fibrinopeptide A] - Homo sapiens (Human)	[P02671]	24
Fibrinogen beta chain precursor [Contains: Fibrinopeptide B] - Homo sapiens (Human)	[P02675]	24
Fibrinogen gamma chain precursor - Homo sapiens (Human)	[P02679]	24
Fibronectin precursor - Homo sapiens (Human)	[P02751]	24
Glyceraldehyde-3-phosphate dehydrogenase - Homo sapiens (Human)	[P04406]	24, 27
Glyceraldehyde-3-phosphate dehydrogenase, testis-specific - Homo sapiens (Human)	[O14556]	24
Gastrin precursor [Contains: Gastrin-71 - Homo sapiens (Human)	[P01350]	24
Gelsolin precursor - Homo sapiens (Human)	[P06396]	24
Glycoprotein hormones alpha chain precursor - Homo sapiens (Human)	[P01215]	24
Glucagon precursor [Contains: Glicentin; Glicentin-related polypeptide - Homo sapiens (Human)	[P01275]	24
Progonadoliberin-1 precursor - Homo sapiens (Human)	[P01148]	24
Stress-70 protein, mitochondrial precursor - Homo sapiens (Human)	[P38646]	24
Glutathione S-transferase A1 - Homo sapiens (Human)	[P08263]	24
Glutathione S-transferase A2 - Homo sapiens (Human)	[P09210]	24
Glutathione S-transferase A3 - Homo sapiens (Human)	[Q16772]	24
Glutathione S-transferase A4 - Homo sapiens (Human)	[O15217]	24
Glutathione S-transferase A5 - Homo sapiens (Human)	[Q7RTV2]	24
Glutathione S-transferase kappa 1 - Homo sapiens (Human)	[Q9Y2Q3]	24
Glutathione S-transferase Mu 1 - Homo sapiens (Human)	[P09488]	24
Glutathione S-transferase Mu 2 - Homo sapiens (Human)	[P28161]	24
Glutathione S-transferase Mu 3 - Homo sapiens (Human)	[P21266]	24
Glutathione S-transferase Mu 4 - Homo sapiens (Human)	[Q03013]	24
Glutathione S-transferase Mu 5 - Homo sapiens (Human)	[P46439]	24
Glutathione transferase omega-1 - Homo sapiens (Human)	[P78417]	24
Glutathione transferase omega-2 - Homo sapiens (Human)	[Q9H4Y5]	24
Glutathione S-transferase P - Homo sapiens (Human)	[P09211]	24
Glutathione S-transferase theta-1 - Homo sapiens (Human)	[P30711]	24
Glutathione S-transferase theta-2 - Homo sapiens (Human)	[P30712]	24
High affinity immunoglobulin epsilon receptor subunit alpha- Homo sapiens (Human)	[P12319]	36
Histone H2A type 2-C - Homo sapiens (Human)	[Q16777]	24
Hemoglobin subunit alpha - Homo sapiens (Human)	[P69905]	24
Hemoglobin subunit theta-1 - Homo sapiens (Human)	[P09105]	24
Hemoglobin subunit zeta - Homo sapiens (Human)	[P02008]	24
Hemoglobin subunit beta - Homo sapiens (Human)	[P68871]	24
Hemoglobin subunit delta - Homo sapiens (Human)	[P02042]	24
Hemoglobin subunit epsilon - Homo sapiens (Human)	[P02100]	24
Hemoglobin subunit gamma-1 - Homo sapiens (Human)	[P69891]	24
Hemoglobin subunit gamma-2 - Homo sapiens (Human)	[P69892]	24
Hemoglobin subunit mu - Homo sapiens (Human)	[Q6B0K9]	24
Sperm protamine-P1 - Homo sapiens (Human)	[P04553]	24
Heat shock 70 kDa protein 1 - Homo sapiens (Human)	[P08107]	24
Heat shock 70 kDa protein 4 - Homo sapiens (Human)	[P34932]	24, 27
Heat shock 70 kDa protein 6 - Homo sapiens (Human)	[P17066]	24
Putative heat shock 70 kDa protein 7 - Homo sapiens (Human)	[P48741]	24
Heat shock cognate 71 kDa protein - Homo sapiens (Human)	[P11142]	24, 27
Heat shock 70 kDa protein 14 - Homo sapiens (Human)	[Q0VDF9]	24
Heat shock protein HSP 90-beta- Homo sapiens (Human)	[P08238]	27
Heat shock protein beta-1 - Homo sapiens (Human)	[P04792]	24
Islet amyloid polypeptide precursor - Homo sapiens (Human)	[P10997]	24
Interferon gamma- Homo sapiens (Human)	[P01579]	35
Interleukin-1 alpha- Homo sapiens (Human)	[P01583]	35
Interleukin-10 precursor - Homo sapiens (Human)	[P22301]	24
Interleukin-12 subunit alpha precursor - Homo sapiens (Human)	[P29459]	24
Interleukin-12 subunit beta precursor - Homo sapiens (Human)	[P29460]	24
Interleukin-15 precursor - Homo sapiens (Human)	[P40933]	24
Interleukin-2 precursor - Homo sapiens (Human)	[P60568]	24
Interleukin-21 precursor - Homo sapiens (Human)	[Q9HBE4]	24
Interleukin-2 receptor alpha chain precursor - Homo sapiens (Human)	[P01589]	24
Interleukin-2 receptor subunit beta precursor - Homo sapiens (Human)	[P14784]	24
Interleukin-4 precursor - Homo sapiens (Human)	[P05112]	24
Interleukin-5 precursor - Homo sapiens (Human)	[P05113]	24
Interleukin-6 precursor - Homo sapiens (Human)	[P05231]	24, 37

Interleukin-8 precursor - Homo sapiens (Human)	[P10145]	24
Insulin precursor [Contains: Insulin B chain; Insulin A chain] - Homo sapiens (Human)	[P01308]	24
Keratin, type I cytoskeletal 18 - Homo sapiens (Human)	[P05783]	24
Keratin, type II cytoskeletal 8 - Homo sapiens (Human)	[P05787]	24
Laminin subunit alpha-1 precursor - Homo sapiens (Human)	[P25391]	24
Laminin subunit alpha-2 precursor - Homo sapiens (Human)	[P24043]	24
Laminin subunit alpha-3 precursor - Homo sapiens (Human)	[Q16787]	24
Laminin subunit alpha-4 precursor - Homo sapiens (Human)	[Q16363]	24
Laminin subunit alpha-5 precursor - Homo sapiens (Human)	[O15230]	24
Laminin subunit beta-1 precursor - Homo sapiens (Human)	[P07942]	24
Laminin subunit beta-2 precursor - Homo sapiens (Human)	[P55268]	24
Laminin subunit beta-3 precursor - Homo sapiens (Human)	[Q13751]	24
Laminin subunit gamma-1 precursor - Homo sapiens (Human)	[P11047]	24
Laminin subunit gamma-2 precursor - Homo sapiens (Human)	[Q13753]	24
Laminin subunit gamma-3 precursor - Homo sapiens (Human)	[Q9Y6N6]	24
Low-density lipoprotein receptor precursor - Homo sapiens (Human)	[P01130]	24
Lupus La protein- Homo sapiens (Human)	[P05455]	38
Galectin-1 - Homo sapiens (Human)	[P09382]	24
Galectin-3 - Homo sapiens (Human)	[P17931]	24
Malate dehydrogenase, mitochondrial- Homo sapiens (Human)	[P40926]	30
Melanoma-associated antigen E1 - Homo sapiens (Human)	[Q9HCI5]	24
Melanoma antigen recognized by T-cells 1 - Homo sapiens (Human)	[Q16655]	24
Pro-MCH-like protein 1 - Homo sapiens (Human)	[Q16048]	24
Pro-MCH-like protein 2 - Homo sapiens (Human)	[Q9BQD1]	24
Macrophage migration inhibitory factor - Homo sapiens (Human)	[P14174]	24
Interstitial collagenase precursor - Homo sapiens (Human)	[P03956]	24
72 kDa type IV collagenase precursor - Homo sapiens (Human)	[P08253]	24
Stromelysin-1 precursor - Homo sapiens (Human)	[P08254]	24
Matrix metalloproteinase-9 precursor - Homo sapiens (Human)	[P14780]	24
Myelin-associated oligodendrocyte basic protein - Homo sapiens (Human)	[Q13875]	24
Myelin-oligodendrocyte glycoprotein precursor - Homo sapiens (Human)	[Q16653]	24
Mucin-1 precursor - Homo sapiens (Human)	[P15941]	24
Myc proto-oncogene protein - Homo sapiens (Human)	[P01106]	24
Myoglobin - Homo sapiens (Human)	[P02144]	24, 39
Myelin proteolipid protein - Homo sapiens (Human)	[P60201]	24
Oxytocin-neurophysin 1 precursor - Homo sapiens (Human)	[P01178]	24
Neurotensin/neuromedin N precursor [Contains: Large neuromedin N - Homo sapiens (Human)	[P30990]	24
Neuropeptide Y precursor [Contains: Neuropeptide Y - Homo sapiens (Human)	[P01303]	24
Myeloperoxidase precursor - Homo sapiens (Human)	[P05164]	24, 40
Phosphatidylinositol-glycan-specific phospholipase D precursor - Homo sapiens (Human)	[P80108]	24
Phosphoglycerate mutase 1- Homo sapiens (Human)	[P18669]	27
Plasminogen precursor - Homo sapiens (Human)	[P00747]	24
Protein disulfide-isomerase/Prolyl 4-hydroxylase subunit beta- Homo sapiens (Human)	[P07237]	27
Protein disulfide-isomerase A5- Homo sapiens (Human)	[Q14554]	27
Protein disulfide-isomerase A3- Homo sapiens (Human)	[P30101]	27
Proteolipid protein 2 - Homo sapiens (Human)	[Q04941]	24
Prostatic acid phosphatase precursor - Homo sapiens (Human)	[P15309]	24
Protamine-2 - Homo sapiens (Human)	[P04554]	24, 41
Protamine-3 - Homo sapiens (Human)	[Q9NNZ6]	24
Parathyroid hormone-related protein precursor - Homo sapiens (Human)	[P12272]	24
Parathyroid hormone/parathyroid hormone-related peptide receptor precursor - Homo sapiens (Human)	[Q03431]	24
Parathyroid hormone precursor - Homo sapiens (Human)	[P01270]	24
Serpin H1 precursor - Homo sapiens (Human)	[P50454]	24
Serum amyloid A protein- Homo sapiens (Human)	[P02735]	42
Sialic acid-binding Ig-like lectin 8/Siglec 8- Homo sapiens (Human)	[Q9NYZ4]	43
Sialic acid-binding Ig-like lectin 9/Siglec 9- Homo sapiens (Human)	[Q9Y336]	31
Small nuclear ribonucleoprotein Sm D1- Homo sapiens (Human)	[P62314]	38
Small nuclear ribonucleoprotein Sm D2- Homo sapiens (Human)	[P62316]	38
Small nuclear ribonucleoprotein Sm D3- Homo sapiens (Human)	[P62318]	38
Somatoliberin precursor - Homo sapiens (Human)	[P01286]	24
Somatostatin precursor - Homo sapiens (Human)	[P61278]	24
60 kDa SS-A/Ro ribonucleoprotein- Homo sapiens (Human)	[P10155]	38
Superoxide dismutase [Cu-Zn] - Homo sapiens (Human)	[P00441]	24
Extracellular superoxide dismutase [Cu-Zn] precursor - Homo sapiens (Human)	[P08294]	24
Superoxide dismutase [Mn], mitochondrial precursor - Homo sapiens (Human)	[P04179]	24

Spectrin alpha chain, erythrocyte - Homo sapiens (Human)	[P02549]	24
Spectrin beta chain, brain 1 - Homo sapiens (Human)	[Q01082]	24
Alpha-synuclein - Homo sapiens (Human)	[P37840]	20, 24
Transforming growth factor beta-1 precursor - Homo sapiens (Human)	[P01137]	24
Transforming growth factor beta-2 precursor - Homo sapiens (Human)	[P61812]	24
Transforming growth factor beta-3 precursor - Homo sapiens (Human)	[P10600]	24
Protein-glutamine gamma-glutamyltransferase K - Homo sapiens (Human)	[P22735]	24
Protein-glutamine gamma-glutamyltransferase 2 - Homo sapiens (Human)	[P21980]	24
Protein-glutamine gamma-glutamyltransferase E precursor - Homo sapiens (Human)	[Q08188]	24
Protein-glutamine gamma-glutamyltransferase 6 - Homo sapiens (Human)	[O95932]	24
Protein-glutamine gamma-glutamyltransferase 4 - Homo sapiens (Human)	[P49221]	24
Protein-glutamine gamma-glutamyltransferase 5 - Homo sapiens (Human)	[O43548]	24
Protein-glutamine gamma-glutamyltransferase Z - Homo sapiens (Human)	[Q96PF1]	24
Prothrombin precursor - Homo sapiens (Human)	[P00734]	24
Talin-1- Homo sapiens (Human)	[Q9Y490]	44
Talin-2- Homo sapiens (Human)	[Q9Y4G6]	44
Thy-1 membrane glycoprotein- Homo sapiens (Human)	[P04216]	45
Thyroglobulin precursor - Homo sapiens (Human)	[P01266]	24
Protachykinin 1 precursor - Homo sapiens (Human)	[P20366]	24
Tubulin beta-4B chain/ Tubulin beta-2 chain- Homo sapiens (Human)	[P68371]	27
Tumor necrosis factor precursor - Homo sapiens (Human)	[P01375]	24
Tumor necrosis factor receptor superfamily member 6/Apo-1 antigen/FASLG receptor- Homo sapiens (Human)	[P25445]	46
Trafficking kinesin-binding protein 1- Homo sapiens (Human)	[Q9UPV9]	27
Tropomyosin alpha-1 chain - Homo sapiens (Human)	[P09493]	24
Tropomyosin beta chain - Homo sapiens (Human)	[P07951]	24
Tropomyosin alpha-3 chain - Homo sapiens (Human)	[P06753]	24
Tropomyosin alpha-4 chain - Homo sapiens (Human)	[P67936]	24
Serotransferrin precursor - Homo sapiens (Human)	[P02787]	24, 39
Lactotransferrin precursor - Homo sapiens (Human)	[P02788]	24
Ubiquitin - Homo sapiens (Human)	[P62988]	24
Vimentin- Homo sapiens (Human)	[P08670]	27
Vinculin	[P18206]	44
VIP peptides precursor [Contains: Intestinal peptide PHV-42; Intestinal peptide PHM-27 - Homo sapiens (Human)	[P01282]	24
Vitronectin precursor - Homo sapiens (Human)	[P04004]	24