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ANALYSIS OF INTERLEUKIN-12 AND INTERLEUKIN-23 PATHWAYS TO DISTINGUISH BETWEEN IMMUNE ACTIVATION AND INFLAMMATION FUNCTIONS

RAZDVAJANJE IZMEĐU IMUNE I INFLAMATORNE AKTIVNOSTI INTERLEUKINA-12 I INTERLEUKINA-23

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Key words

Interleukin-12, Interleukin-23, Cytokine, Immune Response, Inflammation, Resonant Recognition Model.

Ključne reči

Interleukin-12, Interleukin-23, Citokini, Imunitet, Inflamacija, Model Rezonantnog Prepoznavanja.

Abstract

The main organism defence against pathogens is immune system, but unfortunately its activity is always associated with unwanted inflammation. It would be beneficial, if it is possible to understand immune activation and inflammation, as well as to identify parameters that can distinguish between immune activation and inflammation. For that purpose, we have used our own nonconventional, biophysical, theoretical Resonant Recognition Model, which we applied to Interleukin-12 (IL-12) and Interleukin-23 (IL-23) pathways. We have identified the separate parameters for those two pathways, and we assigned them separately to immune activation and inflammation biological functions. These results could be used in diminishing effects of unwanted inflammation in number of health conditions.

INTRODUCTION

Activation of immune system is the one of the most important processes within the body, as it enables organism to fight against pathogens. Sometimes the immune system is activated for no apparent reason, like in autoimmune diseases when it attacks its own body cells. In addition, it can be activated with allergens when it has no body protection role, but it still induces harmful inflammation. In any of those cases the immune system activation is always associated with inflammation which is unwanted, unpleasant, harmful and in some cases could be fatal. Thus, if it is possible to have beneficial immune system activation without associated harmful inflammation, the number of diseases and health conditions, like autoimmune diseases, allergies, infections and even cancer, would be possible to be successfully treated.

Interleukin-12 (IL-12) and Interleukin-23 (IL-23) pathways appear to play a key role in immune system activation and associated inflammation [(1)]. IL-12 is the key factor for inducing innate immune responses and regulating the type and duration of adaptive immune response [(2)]. It plays an important role in the maintenance of tolerance in intestinal mucosa and it is involved in the differentiation of naïve T cells into Th1 cells [(3-4)]. It is known as a T cell-stimulating factor, which can stimulate the growth and function of T cells [(1)]. It also stimulates the production of interferon-gamma and tumour necrosis factor-alpha from T cells and natural killer cells. IL-12 plays an important role in the activities of natural killer cells and T lymphocytes. It is a heterodimeric cytokine encoded by two separate genes: IL-12A (p35) and IL-12B (p40) [(5)]. IL-12B is also associated with IL-23A (p19) to form IL-23, a heterodimeric cytokine

which functions in innate and adaptive immunity [6]. IL-23 binds to receptor complex composed of IL-12Rβ1 and IL-23R [7] and promotes production of proinflammatory cytokines and induces autoimmune inflammation [8-10]. In addition, IL-23 seems to be implicated in profibrotic pathways, as it has been found to upregulate collagen type I mRNA in fibroblasts from patients with systemic sclerosis [11], and to upregulate fibronectin, collagen expression and wound healing rates in human colonic subepithelial myofibroblasts, similarly to TGF-β [12]. Thus, we can simplify that IL-12 pathway is mostly associated with activation of immune system, while IL-23 is more associated with inflammatory pathways. Both IL-12 and IL-23 pathways are presented in Figure 1.

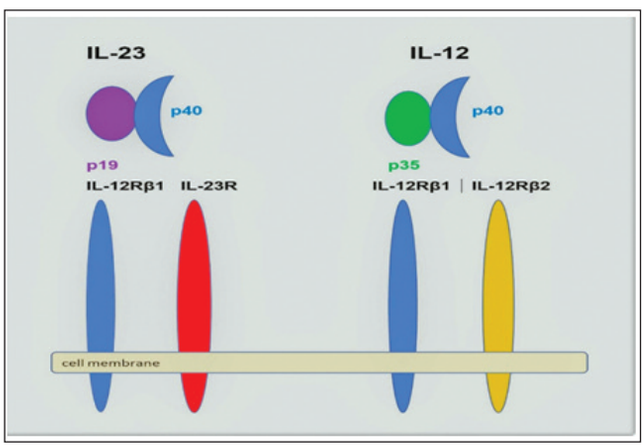

Figure 1. *Graphical presentation of IL-12 and IL-23 pathways.*

Both IL-12 and IL-23 pathways are used as targets for therapy of autoimmune diseases, as well as for immune system stimulation [13]. Ustekinumab is a human monoclonal antibody targeting p40, the common subunit of IL-12 and IL-23, that is used for the treatment of psoriasis and Crohn's Disease [14]. Guselkumab, another antibody targeting IL-23, has been approved by FDA, for use in patients with moderate to severe psoriasis [15], and it is currently under development, at a phase 2/3 clinical study (GALAXI) in patients with moderately to severely active CD (https://clinicaltrials.gov/ct2/show/NCT03466411). Thus, it is extremely important to understand functions of both IL-12 and IL-23 pathways and to distinguish between immune system activation and inflammation as separate functions.

Here, we have utilised our own Resonant Recognition Model (RRM), to distinguish between immune system activation and inflammation functions by analysing both IL-12 and IL-23 pathways. The RRM is based on the findings that certain periodicities within the distribution of energy of delocalized electrons along protein molecules are critical for their biological functions and/or interactions with their targets [16-27]. If charge transfer through protein macromolecules is introduced, then charge moving through macromolecular backbone can produce electromagnetic radiation, absorption and resonance with spectral characteristics corresponding to the energy distribution and charge velocity [16-27].

Once when separate RRM characteristics of immune activation and inflammation have been identified, these characteristics can be used to manipulate IL-12 and IL-23 pathways in such way that would promote immune response without inducing inflammation. Such approach could be extremely useful in diminishing effects of unwanted inflammation within the number of diseases and health conditions, like autoimmune diseases, allergies, infections and even cancer.

METHODS AND MATERIALS

Resonant Recognition Model

Here, we present and use our own nonconventional, biophysical, theoretical Resonant Recognition Model (RRM), which is based on the findings that certain periodicities within the distribution of energy of delocalized electrons along protein molecules are critical for protein biological functions and/or interactions with their targets [16-27]. The RRM model has been extensively published and experimentally successfully tested [16-38]. The RRM model has been presented and well explained in our previous publications as follows:

"All proteins can be considered as a linear sequence of their constitutive elements, i.e. amino acids and biological function of proteins is determined primarily by this linear sequence. The RRM [16-18] interprets this linear information by transforming protein sequence into a numerical series and then into the frequency domain using digital signal processing methods: Fast Fourier Transform (FFT).

Protein primary structure can be presented as a numerical series by assigning the relevant physical parameter value to each amino acid. Our investigations have shown that the best correlation can be achieved with parameters which are related to the energy of delocalised electrons of each amino acid (calculated as Electron Ion Interaction Potential (EIIP)), as electrons delocalised from the particular amino acid, have the strongest impact on the electronic distribution of the whole protein [16-19]. The resulting numerical series represents the distribution of the free electron's energies along the protein molecule.

Such numerical series are then analysed by digital signal analysis methods, using FFT, to extract information pertinent to the biological function. As the distance between amino acid residues in a polypeptide chain is 3.8Å, it can be assumed that the points in the numerical sequence are equidistant. For further numerical analysis, the distance between points in these numerical sequences is set at an arbitrary value of d=1. Therefore, the maximum frequency in the spectrum is F=1/2d=0.5. The total number of points in the sequence influences the resolution of the spectrum only. Therefore, for N-point sequence the resolution in the spectrum is equal to 1/N. The n-th point in the spectral function corresponds to the frequency f=n/N.

To extract common spectral characteristics of sequences having the same or similar biological function, the multiple cross-spectral function is used. Peak frequencies in such a multiple cross-spectral function present common frequency component for all sequences analysed. Such common frequency components are found to be related to the common biological function of the analysed proteins leading to the conclusion that each specific biological function within the protein is characterised by one frequency [16-18,20-21].

Each biological function and/or process is driven by proteins that selectively interact with other proteins, DNA regulatory segments or small molecules. Using the RRM, it has been shown that proteins and their targets share the same matching characteristic frequency [16-18,20-21]. The matching of periodicities within the distribution of energies of free electrons along the interacting proteins can be regarded as the resonant recognition and is highly selective. Thus, the RRM frequencies characterise not only protein function, but also recognition and interaction between a protein and its targets: receptors, binding proteins and inhibitors. In addition, it has been also shown that interacting proteins have opposite phases at their characteristic recognition frequency [16-18,20,22]. Every frequency can be presented by one sinusoid characterised with its frequency, amplitude and phase. The phase is presented in radians and can be between $-\pi$ and $+\pi$ (-3.14 and +3.14). The phase difference of or about 3.14 is considered opposite phase. The phase value can be presented in the phase circle where it is easier to observe graphically opposite phases.

As it has been proposed that the RRM frequencies characterize, not only a general function, but also a recognition and interaction between the macromolecule and its target, which then can be considered as resonant recognition. This could be achieved with resonant energy transfer between the interacting macromolecules through oscillations of a physical field, which is electromagnetic in nature. Since there is evidence that proteins have certain conducting or semi-conducting properties, a charge moving through the macromolecular backbone and passing different energy stages, caused by different amino acid or nucleotide side groups, can produce sufficient conditions for a specific electromagnetic radiation or absorption. The frequency ranges of this field depend on the charge velocity. The RRM proposes, based on solid state physics principles, that the charge is travelling through the macromolecular backbone at the estimated velocity of 7.87×10^5m/s [23,24]. For this velocity and with the distance between amino acids in a protein molecule of 3.8Å, the frequency of protein interactions was estimated to be in the range between 10^{13}Hz and 10^{15}Hz. Therefore, the estimated frequency range for both amino acid and nucleotide macromolecules includes infra-red, visible and ultra-violet light. To support this idea, we compared our RRM computational predictions for variety of biological functions with number of published experimental results [16-18]:

- Laser light growth promotion of cells, by using the frequencies of light to produce the similar effect to that of growth factor proteins;
- Chymotrypsin activation (increase of enzyme activity) achieved by laser light radiation in a range of 850-860nm;
- Activation of highly homologous plant photoreceptors which, although being very homologous, absorb different wavelengths of light;
- Photo activated proteins, e.g. rhodopsin, flavodoxin, etc.

These comparisons have shown a strong linear correlation between frequencies, as calculated using the RRM method and experimentally measured characteristic frequencies, with the slope factor of K=201 [16-18,25]. This finding parallel with the frequency range previously associated with the RRM numerical frequency spectrum that has been calculated from the charge velocities through the protein backbone. This correlation can be represented as following:

$$\lambda = K / frrm$$

where λ is the wavelength of light irradiation in nm, which can influence particular biological process, frrm is RRM numerical frequency and K is coefficient of this linear correlation.

We applied this concept on number of proteins and DNA examples [19-30]. The concept has been also experimentally tested by predicting the electromagnetic frequencies for L-Lactate Dehydrogenase [27], where by radiating L-Lactate Dehydrogenase with predicted calculated electromagnetic frequencies the significant change in enzyme activity was achieved. The concept has also been tested independently on experimental measurements of photon emission from dying melanoma cells [28], on photon emission from lethal and non-lethal Ebola strains [29], as well as on classic signalling pathway, JAK-STAT, traditionally composed of nine sequential protein interactions [30].

Keeping all this in mind, we propose that the RRM concept is excellent predictor for proteins selective interactions, biological processes and pathways in living cells. In our previous work, we have calculated large number of specific frequencies for different protein and DNA biological functions and interactions [16-27,31-38].

Once the characteristic frequency for biological function of the protein is identified, it is possible to design new proteins with desired frequency components and consequently with desired biological functions[16-18,20,32-33]. This approach has been already successfully applied and experimentally tested in design of FGF analogue [16-18,33], HIV envelope protein analogue[16-18,22,34-35], IL-12 analogue [36] and peptide to mimic myxoma virus oncolytic function [37-38]."

Protein Sequences

The following protein sequences have been analysed using RRM from UniProt database:

Fifteen interleukin-12 alpha proteins:

>sp|P54349|IL12A_BOVIN Interleukin-12 subunit alpha OS=Bos taurus OX=9913 GN=IL12A PE=2 SV=1

>sp|P29459|IL12A_HUMAN Interleukin-12 subunit alpha OS=Homo sapiens OX=9606 GN=IL12A PE=1 SV=2

>sp|P43431|IL12A_MOUSE Interleukin-12 subunit alpha OS=Mus musculus OX=10090 GN=Il12a PE=1 SV=1

>sp|Q9TU27|IL12A_SHEEP Interleukin-12 subunit alpha OS=Ovis aries OX=9940 GN=IL12A PE=1 SV=1

>sp|Q29053|IL12A_PIG Interleukin-12 subunit alpha OS=Sus scrofa OX=9823 GN=IL12A PE=2 SV=2

>sp|P48091|IL12A_MACMU Interleukin-12 subunit alpha OS=Macaca mulatta OX=9544 GN=IL12A PE=2 SV=1

>sp|Q9XSQ6|IL12A_HORSE Interleukin-12 subunit alpha OS=Equus caballus OX=9796 GN=IL12A PE=2 SV=1

>sp|O02814|IL12A_CAPHI Interleukin-12 subunit alpha OS=Capra hircus OX=9925 GN=IL12A PE=2 SV=1

>sp|Q28267|IL12A_CANLF Interleukin-12 subunit alpha OS=Canis lupus familiaris OX=9615 GN=IL12A PE=2 SV=1

>sp|Q865X0|IL12A_LAMGL Interleukin-12 subunit alpha OS=Lama glama OX=9844 GN=IL12A PE=2 SV=1

>sp|Q28233|IL12A_CEREL Interleukin-12 subunit alpha OS=Cervus elaphus OX=9860 GN=IL12A PE=2 SV=1

>sp|Q9R103|IL12A_RAT Interleukin-12 subunit alpha OS=Rattus norvegicus OX=10116 GN=Il12a PE=2 SV=1

>sp|Q865Y2|IL12A_PAPAN Interleukin-12 subunit alpha OS=Papio anubis OX=9555 GN=IL12A PE=2 SV=2

>sp|Q91ZK6|IL12A_SIGHI Interleukin-12 subunit alpha OS=Sigmodon hispidus OX=42415 GN=IL12A PE=2 SV=1

>sp|Q2PE77|IL12A_BUBCA Interleukin-12 subunit alpha OS=Bubalus carabanensis OX=346063 GN=IL12A PE=2 SV=1

Fourteen interleukin-12 beta proteins:

>sp|Q924V5|IL12B_CAVPO Interleukin-12 subunit beta OS=Cavia porcellus OX=10141 GN=IL12B PE=2 SV=1

>sp|P48095|IL12B_MACMU Interleukin-12 subunit beta OS=Macaca mulatta OX=9544 GN=IL12B PE=2 SV=1

>sp|P29460|IL12B_HUMAN Interleukin-12 subunit beta OS=Homo sapiens OX=9606 GN=IL12B PE=1 SV=1

>sp|Q28938|IL12B_PIG Interleukin-12 subunit beta OS=Sus scrofa OX=9823 GN=IL12B PE=2 SV=1

>sp|P46282|IL12B_BOVIN Interleukin-12 subunit beta OS=Bos taurus OX=9913 GN=IL12B PE=2 SV=1

>sp|P43432|IL12B_MOUSE Interleukin-12 subunit beta OS=Mus musculus OX=10090 GN=Il12b PE=1 SV=1

>sp|Q28268|IL12B_CANLF Interleukin-12 subunit beta OS=Canis lupus familiaris OX=9615 GN=IL12B PE=2 SV=1

>sp|Q28234|IL12B_CEREL Interleukin-12 subunit beta OS=Cervus elaphus OX=9860 GN=IL12B PE=2 SV=1

>sp|Q9XSQ5|IL12B_HORSE Interleukin-12 subunit beta OS=Equus caballus OX=9796 GN=IL12B PE=2 SV=1

>sp|O02744|IL12B_FELCA Interleukin-12 subunit beta OS=Felis catus OX=9685 GN=IL12B PE=2 SV=1

>sp|Q865W9|IL12B_LAMGL Interleukin-12 subunit beta OS=Lama glama OX=9844 GN=IL12B PE=2 SV=1

>sp|Q91ZK7|IL12B_SIGHI Interleukin-12 subunit beta OS=Sigmodon hispidus OX=42415 GN=IL12B PE=2 SV=1

>sp|Q865Y3|IL12B_PAPAN Interleukin-12 subunit beta OS=Papio anubis OX=9555 GN=IL12B PE=2 SV=1

>sp|Q866G3|IL12B_BUBBU Interleukin-12 subunit beta OS=Bubalus bubalis OX=89462 GN=IL12B PE=2 SV=1

Six interleukin-12 receptor proteins:

>sp|P42701|I12R1_HUMAN Interleukin-12 receptor subunit beta-1 OS=Homo sapiens OX=9606 GN=IL12RB1 PE=1 SV=1

>sp|P97378|I12R2_MOUSE Interleukin-12 receptor subunit beta-2 OS=Mus musculus OX=10090 GN=Il12rb2 PE=1 SV=1

>sp|Q99665|I12R2_HUMAN Interleukin-12 receptor subunit beta-2 OS=Homo sapiens OX=9606 GN=IL12RB2 PE=1 SV=1

>sp|Q60837|I12R1_MOUSE Interleukin-12 receptor subunit beta-1 OS=Mus musculus OX=10090 GN=Il12rb1 PE=1 SV=2

>sp|Q9BEG2|I12R2_BOVIN Interleukin-12 receptor subunit beta-2 OS=Bos taurus OX=9913 GN=IL12RB2 PE=2 SV=1

>sp|Q8MJS1|I12R2_PIG Interleukin-12 receptor subunit beta-2 OS=Sus scrofa OX=9823 GN=IL12RB2 PE=2 SV=1

Six interleukin-23 proteins:

>sp|Q9NPF7|IL23A_HUMAN Interleukin-23 subunit alpha OS=Homo sapiens OX=9606 GN=IL23A PE=1 SV=1

>sp|Q9EQ14|IL23A_MOUSE Interleukin-23 subunit alpha OS=Mus musculus OX=10090 GN=Il23a PE=1 SV=1

>sp|Q9N2H9|IL23A_PIG Interleukin-23 subunit alpha OS=Sus scrofa OX=9823 GN=IL23A PE=3 SV=1

>sp|Q91Z84|IL23A_RAT Interleukin-23 subunit alpha OS=Rattus norvegicus OX=10116 GN=Il23a PE=2 SV=1

>sp|Q64FU1|IL23A_HORSE Interleukin-23 subunit alpha OS=Equus caballus OX=9796 GN=IL23A PE=3 SV=1

>sp|Q6LA37|IL23A_CAVPO Interleukin-23 subunit alpha OS=Cavia porcellus OX=10141 GN=IL23A PE=2 SV=1

Two interleukin-23 receptor proteins:

>sp|Q5VWK5|IL23R_HUMAN Interleukin-23 receptor OS=Homo sapiens OX=9606 GN=IL23R PE=1 SV=3

>sp|Q8K4B4|IL23R_MOUSE Interleukin-23 receptor OS=Mus musculus OX=10090 GN=Il23r PE=2 SV=1

Six active cleaved human interleukin-12 and interleukin-23 proteins and receptors:

>sp|P29459|IL12A_HUMAN active 23-219 Interleukin-12 subunit alpha OS=Homo sapiens OX=9606 GN=IL12A PE=1 SV=2

>sp|P29460|IL12B_HUMAN active 23-328 Interleukin-12 subunit beta OS=Homo sapiens OX=9606 GN=IL12B PE=1 SV=1

>sp|P42701|I12R1_HUMAN active 24-662 Interleukin-12 receptor subunit beta-1 OS=Homo sapiens OX=9606 GN=IL12RB1 PE=1 SV=1

>sp|Q99665|I12R2_HUMAN active 24-862 Interleukin-12 receptor subunit beta-2 OS=Homo sapiens OX=9606 GN=IL12RB2 PE=1 SV=1

>sp|Q9NPF7|IL23A_HUMAN active 20-189 Interleukin-23 subunit alpha OS=Homo sapiens OX=9606 GN=IL23A PE=1 SV=1

>sp|Q5VWK5|IL23R_HUMAN active 24-629 Interleukin-23 receptor OS=Homo sapiens OX=9606 GN=IL23R PE=1 SV=3

RESULTS

Here, we have utilised RRM to analyse IL-12 and IL-23 pathways, with the aim to find out the RRM characteristics for activation of immune system (IL-12 pathway) and inflammation (IL-23 pathway).

RRM Characteristics of IL-12 Pathway

IL-12 pathway consists of p35 and p40 IL-12 subunits, which are interacting with receptors: IL-12Rβ1 and IL-12Rβ2, as presented in Figure 1 on the right.

When all proteins involved in IL-12 pathway, including IL-12A, IL-12B, IL-12Rβ1 and IL-12Rβ2 proteins, from UniProt database, as listed in Materials, are analysed using the RRM approach, the common characteristic frequency was found to be at f1=0.4531±0.0051, as presented in Figure 2. According to RRM principles as described above, frequency f1 represents electromagnetic radiation wavelength of 444nm, which is within the visible violet light spectrum. This result is in accordance with previously obtained RRM characteristic frequency for IL-12 pathway [31], which is here more prominent as more proteins are available and taken into account. Having in mind the specific biological function of IL-12 pathway, we propose that frequency f1 is characterising immune response activation.

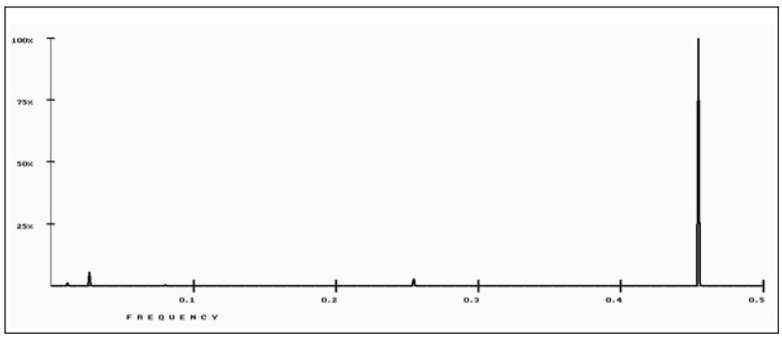

***Figure 2**. RRM cross-spectrum of fifteen IL-12A proteins, fourteen IL-12B proteins, two IL-12Rβ1 proteins and four IL-12Rβ2 proteins. The common characteristic frequency is at f1=0.4531±0.0051, which represents electromagnetic radiation wavelength of 444nm.*

RRM Characteristics of IL-23 Pathway

IL-23 pathway consists of p19 and p40 IL-23 subunits, which are interacting with receptors: IL-12Rβ1 and IL-23R, as presented in Figure 1 on the left. Although, the part of IL-23 pathway (p40 subunit and receptor IL-12Rβ1) is identical to part of IL-12 pathway, these two pathways have different biological functions.

When all proteins involved in IL-23 pathway, including IL-23A, IL-12B, IL-12Rβ1 and IL-23R proteins, from UniProt database, as listed in Materials, are analysed using the RRM approach, the common characteristic frequency was found to be at f2=0.2275±0.0051, as presented in Figure 3. According to RRM principles as described above, frequency f2 represents electromagnetic radiation wavelength of 884nm, which is within the infrared spectrum. Having in mind that IL-23 pathway is associated with inflammation, we propose that frequency f2 is characterising inflammation process.

Thus, we propose that frequency f1=0.4531±0.0051 (444nm) is characterising IL-12 pathway, presented in Figure 1 on the right, and thus is characterising activation of immune system, while frequency f2=0.2275±0.0051 (884nm) is characterising IL-23 pathway, presented in Figure 1 on the left, and thus is characterising inflammation.

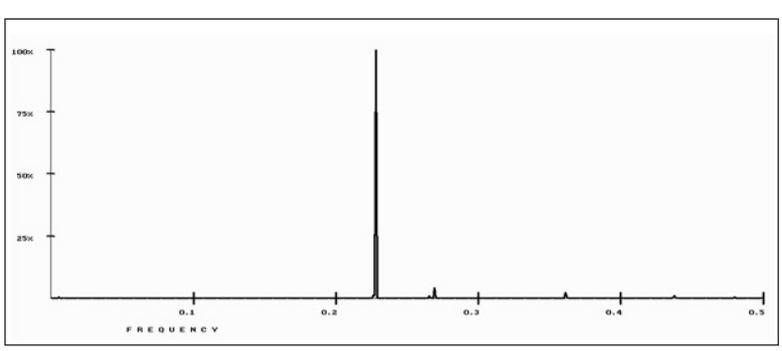

***Figure 3.** RRM cross-spectrum of six IL-23A proteins, six IL-12B proteins, two IL-12Rβ1 proteins and two IL-23R proteins. The common characteristic frequency is at f2=0.2275±0.0051, which represents electromagnetic radiation wavelength of 884nm.*

RRM Phases for Specific Interactions within Human IL-12 and IL-23 Pathways

According to RRM principles, as described above, for the interaction between protein and its receptor, apart from the common frequency, it is necessary to have approximately opposite phases, more opposite indicates better interaction. To analyse the specific interaction between participating proteins in both pathways, we concentrate on human proteins involved in both IL-12 and IL-23 pathways, including IL-12A, IL-12B, IL-12Rβ1, IL-12Rβ2, IL-23 and IL-23R, with the aim to find out phases at RRM characteristic frequency f1 for those involved in IL-12 pathway and phases at RRM characteristic frequency f2 for those involved in IL-23 pathway, as presented in Table 1 and within phase circles in Figure 4.

***Table 1.** Phases at RRM characteristic frequency f1 for those involved in IL-12 pathway and phases at RRM characteristic frequency f2 for those involved in IL-23 pathway.*

Protein/Frequency	f1=0.4531	Delta with IL-12A	f2=0.2275	Delta with IL-12B
IL-12A human	+3.05			
IL-12B human	+1.54	1.51	+0.34	
IL-12Rβ1 human	+0.07	2.98	+2.75	2.41
IL-12Rβ2 human	+0.50	2.55		
IL-23 human			-2.57	2.91
IL-23R human			+2.92	2.58

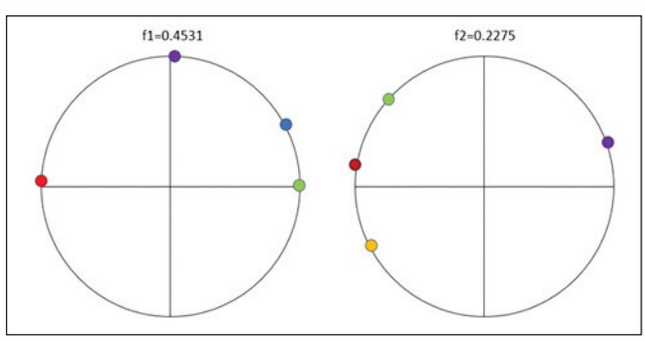

***Figure 4.** Phases for human proteins involved in IL-12 pathway for frequency f1 on the left and phases for human proteins involved in IL-23 pathway for frequency f2 on the right. The colour of each phase corresponds to the colour of proteins in Table 1.*

As it is proposed within RRM approach that for successful interaction, it is necessary to have approximately opposite phases at the frequency characterising this interaction, we can observe from Table 1 and Figure 4 that:

- within IL-12 pathway the most probable direct interaction is between IL-12A and both receptors IL-12Rβ1 and IL-12Rβ2,
- within IL-23 pathway the most probable direct interaction is between IL-12B and both receptors IL-12Rβ1 and IL-23R, as well as IL-23.

DISCUSSION

The activation of immune system, which is critical for organism survival and its fight against pathogens always comes associated with unwanted and harmful inflammation. Thus, it is important to understand how immune system is activated and to distinguish between immune system activation and inflammation. Key pathways within these processes are IL-12 and IL-23 pathways, as presented in Figure 1. It has been proposed that IL-12 pathway is mainly associated with immune system activation, while IL-23 pathway is mainly associated with inflammation although half of the proteins (p40 and IL-12Rβ1) involved in these pathways are common [(1)]. The cross similarity between these two pathways cause difficulties to distinguish between their different functions: immune activation and inflammation, using conventional methods.

Here, we have utilised our own nonconventional, biophysical, theoretical RRM approach, which is based on the findings that certain periodicities within the distribution of energy of delocalised electrons along protein are critical for its biological function, to analyse IL-12 and IL-23 pathways. The aim was to find out the RRM characteristics for activation of immune system (IL-12 pathway) and inflammation (IL-23 pathway). After analysing proteins involved within these two pathways, we have identified distinct RRM characteristic frequencies: for IL-12 pathway at f1=0.4531±0.0051 (444nm), as presented in Figure 2 and for IL-23 pathway at f2=0.2275±0.0051 (884nm) as presented in Figure 3. The fact that distinct frequencies have been identified for IL-12 and IL-23 pathways, although they share half of involved proteins, provides the opportunity to observe separately immune activation and inflammation processes.

To confirm specific interactions at these RRM characteristic frequencies, we have calculated phases at these characteristic frequencies for all human proteins participating within these two separate pathways, as presented in Table 1 and Figure 4. The fact that we have found opposite phases for interacting proteins at characteristic frequencies for both pathways is, according to RRM principles, the confirmation that identified RRM characteristic frequencies f1 and f2 are indeed characterising interactions and functions within IL-12 and IL-23 pathways. This is for the first time, that specific but different characteristics for immune activation and inflammation have been identified and thus it is possible to distinguish between these two biological processes.

CONCLUSION

Results presented here, open possibility for separately considering immune activation and inflammation as independent biological functions. This provides opportunity for inducing immune activation and independently diminishing inflammation, either by electromagnetic radiation of predicted wavelengths or by designing peptides having the specific predicted RRM frequencies and phases. This new approach opens new possibilities in treating autoimmune diseases, allergies, infections and even cancer.

Sažetak

Imunitet je glavna odbrana organizma protiv patogena, ali je nazalost uvek povezan sa nezeljenom inflamacijom. Bilo bi znacajno da se razume proces aktiviranja imunog sistema i proces inflamacije sa idejom da se odrede parametri koji mogu da naprave razliku izmedju ta dva procesa. U tom smislu smo upotrebili nas nekonvencionalni, biofizicki, teoretski Model Rezonantnog Prepoznavanja, koji smo primenili na Interleukin-12 (IL-12) i Interleukin-23 (IL-23) bioloske signale. Odredili smo posebne parametre za ta dva bioloska signala i odvojeno smo ih pripisali procesu aktiviranja imunog sistema i procesu inflamacije. Nasi rezultati mogu da se upotrebe za smanjenje uticaja nezeljene inflamacije u velikom broju zdravstvenih problema.

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