Chapter

Introductory Chapter: Cytokines - The Diamonds and Pearls of Biological Systems

Márió Gajdács and Payam Behzadi

1. The historical background of immunology

When we are reading or investigating the topics of cellular and molecular immunology including cytokines, our unconscious mind suddenly goes back to the Iranian "Immunologist King," Mithridates VI Eupator of Pontus. Pontus is a Greek term referring to the Sea; but conceptually – in accordance with geographic evidences of that time period – it refers to the Black Sea. Indeed, he is known as the first immunologist in the ancient world [1–4].

Mithridates VI Eupator of Pontus (reigned 120–163 BC), the son of Mithridates V Euergetes, was proud over his Iranian heritage and ruled the Pontus region (Asia Minor, The Great Persia Empire Region; Present-day Turkey) throughout the Hellenistic and Mithridatic Kingdoms. Despite accepting Hellenism, he always considered himself as an Iranian king from royal Achaemenid lineages. Indeed, his Iranian origin went back as far as Darius I and Cyrus the Great (The King of Kings). His name Mithridates depicts the God of Light (Mithradatha: sent (given) by Mithra, the ancient Iranian God of Sun) [1, 2, 5–7].

Mithridates VI Eupator of Pontus is the founder of the *Mithridatism* theory which refers to the phenomenon of acquired immunity against poisons, by using determined doses of the poison to expose the individual to the agent little by little [8]. Hence, he used cocktails of antidotes against currently known poisons every day. The potion of Mithridates VI Eupator of Pontus was a mixture of 54 currently known poisons which was termed "**Antidotum Mithridaticum.**" His popular poisonous potion was consumed by people from all walks of life for about two millennia [6, 9, 10]. This process is very similar to the act of vaccination and may be considered as a preliminary form of preventive medicine [11].

Mithridates VI Eupator of Pontus was a genius because he was not only an exceptional expert in immunization and toxicology, but he could also talk in 22–25 different languages. Moreover, he was interested in medicine and pharmacology; therefore, Mithridates VI Eupator of Pontus has written several treatises regarding the characteristics of "**materia medica**" together with the related cases. These invaluable Mithridatic treatises were translated into Latin between 95 and 25 BC by Lenaeus, which were recognized as unique and effective prescriptions in Rome [12].

He was a researcher in the fields of immunology, toxicology, pharmacology, and medicine [4, 11, 12]. Due to this fact, the Iranian king, Mithridates VI Eupator of Pontus is a shining star in the treasure of science and history of Iran.

2. The immune system and cytokines

After about 2000 years, the basis of our knowledge and understanding of the immune system and immunity is very similar; however, what has changed is our ability to have an invaluable interpretation from our scientific observations.

The progression of cellular and molecular biology, together with bioinformatics, computational biology, and medicinal chemistry has given us an opportunity to have an effective understanding of the role of versatile molecules, proteins, and glycoproteins in different fields of immunology.

As we know today, the immune system is a complex network, containing wide range of cells and molecules which works rigorously and around the clock. The main sections of the immune system are divided into the innate and adaptive immune structures, while at the same time they create a unite and interdependent complex.

The unity of innate and adaptive immune system is supported by the diversity of common molecules, cells, mechanisms, processes, and pathways. However, the innate immune system is activated first and by the continuous of the presence of the unknown antigen(s), the adaptive immune system will be activated, usually a few days later. Besides, B- and T- lymphocytes have pivotal roles in maintaining the adaptive immune system and a long-lasting immune response [13].

The immune system – whether innate or adaptive– employs versatile mechanisms to protect the host's body from various "invaders," including pathogens or any other agents which may cause any type of disease. In this regard, the proteins of cytokines and chemokines are produced by different activated immune and non-immune cells and cell receptors, which they convoke a mass of molecules and cells into the center of infection [13].

Therefore, cytokines are noteworthy molecules, with a diversity of activities, functions, structures, and potential abilities. Due to this characteristic of cytokines makes them like "diamonds" and "pearls" of the immune system. Cytokines are invaluable treasure of the immune system with a high plasticity in functions and structures.

They join not only the all parts of the immune system together and unite them as a whole, but also the cytokines contribute in non-immune cells and molecules to orchestrate different cells, tissues, organs, and systems. That is why we may call cytokines as diamonds and pearls of the biological systems.

3. Immune system and cytokines

Cytokines were first described as soluble pyrexins by Menkin in 1944 [14]. The term "cytokine" was proposed (coined) by Cohen et al. through their commentary, published in 1974 [15, 16].

From that point onward, our knowledge regarding cytokines increased significantly. Therefore, in 1978, more than 100 different types activities were described, in association with cytokines [14].

Cytokines comprise a diverse group of proteins and glycoproteins, with molecular weights ranging between 5 and 20 kDa [17, 18]. These amazing molecules contribute to different biological and physiological mechanisms, such as blood pressure, inflammation, and cellular metabolism [18, 19]. Cytokines act locally, and therefore, they affect their peripheral cells in a paracrine style and the producing cells in an autocrine manner. Those cytokines, which disseminate via blood stream across the body act in an endocrine fashion, similarly to hormones. Due to this fact, there are no clear differences between hormones and cytokines, and the employed

molecules by different biologic systems involving endocrine functions, hematopoiesis, immunity, and the nerves have similar characteristics in their functions and structures [13, 14, 16]. In another words, cytokines orchestrate hematopoietic, immune, and non-immune cells of the host in their development, differentiation, function, growth, and regulation, throughout the employment of paracrine and autocrine signaling pathways [13, 16, 19, 20]. Indeed, cytokines regulate, modulate, and orchestrate biological systems, for example, innate and adaptive immune system networks by induction of their own secretion [13]. In this regard, the Human Genome Project (HGP) has had an important role to recognize the different types of cytokines and their association with health and diseases [19]. The homeostasis across the systems of the human body is provided by an influent balance between anti-inflammatory and pro-inflammatory cytokines. Hence, the expression of genes producing cytokines is entirely modulated by long non-coding RNAs, both in transcriptional and post-transcriptional phases [18].

Cytokines are multifunctional proteins with a versatile of receptors, which are distributed in different systems of the body. Therefore, they can be categorized in accordance with variety plethora of criteria. However, it is recommended that the cytokines' classification would be on the basis of their receptors [16, 21]. Cytokines activate the related signaling pathway by their specific intracellular signaling cascades [13]. The major superfamilies of cytokine receptors are consisting of Transforming Growth Factor-β (TGF-β), Tumor Necrosis Factor (TNF) receptor, Serine Kinases family, Receptor Tyrosine kinases, Interleukin-1 (IL-1) and the related Toll-like Receptors (TLR), IL-17 receptors Type II (interferon), and Type I (hematopoietin) [16]. The chemokine receptor includes the G protein-coupled receptor family [19].

The type I receptor family, which is known as the hematopoietin receptor family, receives different types of cytokines including IL-2, IL-3, IL-4, IL-5 IL-6, IL-7, IL-9, IL-11, IL-12, IL-13, IL-15, IL-21, IL-23, IL-27, IL-31, IL-35, growth hormone (GH), prolactin (PRL), erythropoietin (EPO), thrombopoietin (TPO), leptin, granulocyte colony stimulating factor (G-CSF), ciliary neurotrophic factor (CNTF), leukemia inhibitory factor (LIF), oncostatin M (OM), cardiotropin-1 (CT-1), granulocyte macrophage (MΦ) colony stimulating factor (GM-CSF), and thymic stromal lymphopoietin (TSLP) [16]. Type I receptor family is structurally composed of homo- or heterodimers [19].

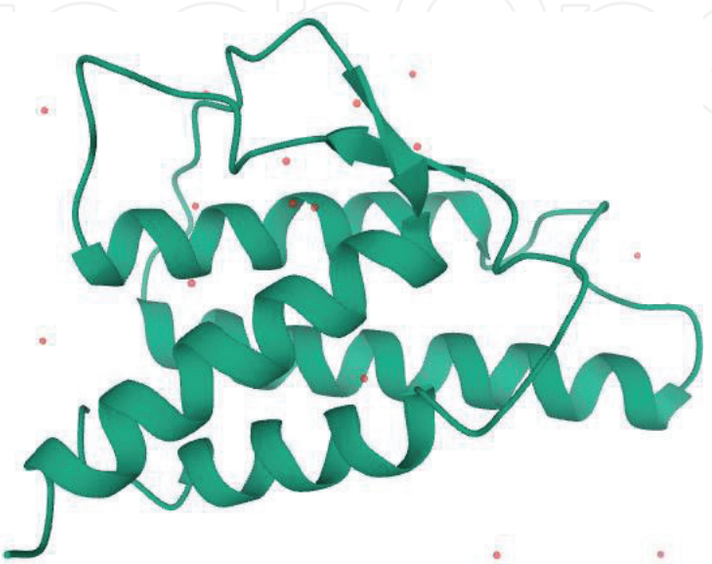

Figure 1.
The structure of IL-4 in details 1HIK PDB file [22, 23].

The type I cytokines are similar in their protein structure, with four anti-parallel α-helices with a configuration of up-up and down-down arrangement. The helices are connected with two long loops and one short loop [16]. This structure is shown in IL-4 (**Figure 1**) [22].

Type II receptor family or interferons (IFNs) with their homo- and heterodimeric structures have high affinity for their ligands, including IFN-α/β, IFN-γ, IL-10, IL-19, IL-20, IL-22, IL-24, IL-26, IL-28, IL-29, and IL-30 [16, 19].

The single pass membrane receptors of IL-1/TLRs bind to cytokines of IL-1α/β, IL-18, IL-33, IL-36, IL-37, and IL-38 [16, 19].

The IL-17 and TGF-β receptor serine kinase families bind to IL-7 and TGF-β cytokines, respectively [16].

The receptor tyrosine kinases, which phosphorylate tyrosine residues bind to a wide range of cytokines including IL-3, IL-16, IL-32, stem cell factor (SCF) and CSF-1, and FMS-like tyrosine kinase 3 (FLT-3) ligand [16, 19].

4. Cytokines and signaling pathways

Cytokines originate from the flat sac organelles of the Golgi-apparatus. These biological diamonds and pearls may have four different predestinations, including soluble cytokines released from endoplasmic reticulum, cytokines linked to the plasma membranes, intracellular cytosolic cytokines, and nuclear cytokines, and the latter group controls the process of transcription [19].

Regulation of cytokines may occur in different pathways, such as transcriptional and post-transcriptional regulations. At transcriptional level, the presence of several transcription factors determines the level of cytokine expression and production. In contrast to transcriptional regulation, the post-transcriptional regulation determines the duration of cytokines' expression. Moreover, the type of cytokines' glycosylation determines their functions and activity [18, 19, 24, 25].

As mentioned previously, there are several types of receptors which bind secreted cytokines. Due to this fact, the related receptors based on their signaling pathway are divided into four receptor groups. The first receptor group is in association with nuclear factor (NF)-κB and mitogen-activated protein kinases (MAPK); the second group involves receptors which employs Smad-family transcription factors; the third category of receptors activates the Ras extracellular signal-regulated kinase (ERK) pathway; and the fourth group which involves the majority of receptors uses the Janus kinase and signal transducers and activators of transcription (JAK-STAT) pathway [26].

The JAK family is composed of four members including JAK1, JAK2, JAK3, and TYK2, which are known as non-receptor multi-domain tyrosine kinases and recognized within the cell's cytoplasm [27, 28]. On the other hand, activation of JAK family members may lead to phosphorylation of tyrosine residues which belong to intracellular domains of the cytokine receptor. The STAT links to phosphorylated tyrosine residues of cytokine receptors. By STAT phosphorylation, the STAT allows for the ability of dimerization, transmission into the nucleus. Furthermore, the STAT will be able to manage the process of gene regulation [27–29].

These interactions reveal the importance of different cytokines, cytokines receptors, and cytokine signaling pathways; in which, the occurrence of any mutation may lead to different immune and non-immune disorders and diseases. Hence, in accordance with complicated interactions and communications in cytokines network, we can understand that recognition of cytokines, cytokine receptors, and their signaling pathways in details may lead us to a great opportunity for definite treatment of the immune and non-immune disorders.

We can conclude that, although Mithridates VI Eupator of Pontus as an Iranian Immunologist/Toxicologist/Pharmacologist King never had an idea about these biological "diamonds" and "pearls" regarded as cytokines, their receptors, and signaling pathway, he was aware of the harmonic communications between organs and systems within the human body.

Conflict of interest

The authors declare no conflict of interest, monetary or otherwise. The authors alone are responsible for the content and writing of this article.

Author details

Márió Gajdács[1,2] and Payam Behzadi[3]*

1 Department of Pharmacodynamics and Biopharmacy, Faculty of Pharmacy, University of Szeged, Szeged, Hungary

2 Institute of Medical Microbiology, Faculty of Medicine, Semmelweis University, Budapest, Hungary

3 Department of Microbiology, College of Basic Sciences, Shahr-e-Qods Branch, Islamic Azad University, Tehran, Iran

*Address all correspondence to: behzadipayam@yahoo.com

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