ISSN:0975-3583,0976-2833 VOL12,ISSUE06,2021

Types of cytokines and their role in some pathological conditions in humans : A review

Fidan Fikrat Ahmed[1]*, Ayoub Ali Hussein[1], Kasim Sakran Abass[2]
[1]Northern Technical University, Health and Medical Technical College/ Medical Laboratory Techniques, Kirkuk, Iraq
[2]Department of Pharmacology and Toxicology, College of Pharmacy, University of Kirkuk, Iraq

*Corresponding authors email: fidanfikrat1972@ntu.edu.iq

Abstract
The cytokines describe as small proteins produced and released by some cells possess a specific impact on interactions and connections between the body cells. The cytokines act as intercellular orders and messengers in the immune response. The cytokines include the types of interferons, the types of interleukins, tumor necrosis factor, the mesenchymal growth factors, and adipokines. In the response to different stimuli, cytokines are released and secreted from different types of cells inclusive leucocytes. Cytokines are an important role in the differentiation of immune cells, inflammation process, development of angiogenesis with tumorigenesis, etc. This current review will highlight the effect of cytokines types in different physiological roles and immune responses.
Keywords: cytokines; interferon; interleukins.

Introduction

The cytokines history was back to the last century after the interferon types were discovered. The cytokines define as pleiotropic proteins and/or small molecules of glycoproteins and their molecular weight is less than 30 kDa (about <200 amino acids). The cytokines are synthesis and produced by different types of cells, like agranular cells that regulate the immunity and inflammation with the process of hematopoiesis (Deverman and Patterson, 2009; Gulati et al., 2016). Approximately 200 cytokines are identified. They possess a high level of a structure called α helical and the molecules participate in the same fold of polypeptide with 4 bundles of α helical structure. Cytokines are classified according to they are synthesis either from the Th1 cells and/or Th2 cells (Figure 1). The Treg cells type 1 (Tr1) was secrete interleukin-10 and Interferon gamma (IFN-γ), interleukin-5 and TGF-β and interleukin-2. Treg cell type 3 (Tr3) syntheses and produces TGF-β and interleukin-10 (Zídek et al., 2009). Based on their production and secretion they are categorized into lymphokines, proinflammatory cytokines, growth factors, chemokines, and anti-inflammatory cytokines (Barnes, 2008).

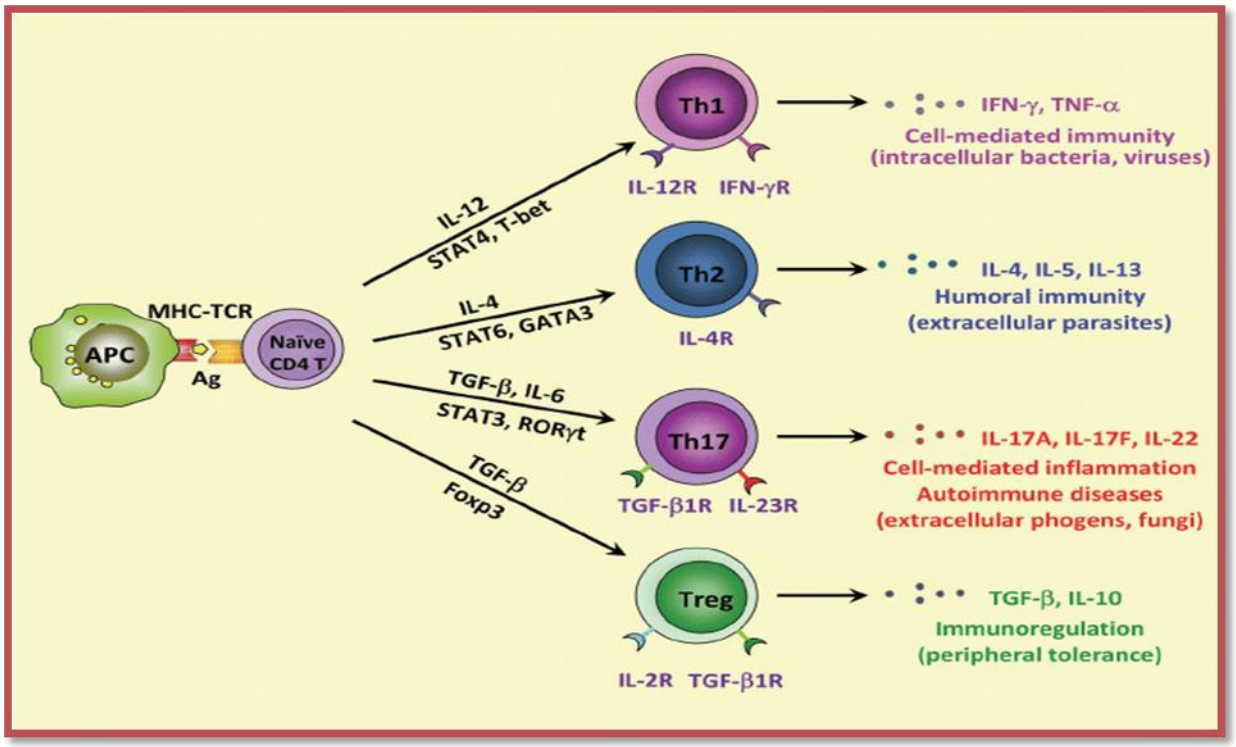

Figure (1): The differentiation of the naive T-cells, from (Leung et al., 2010).

ISSN:0975-3583,0976-2833 VOL12,ISSUE06,2021

Cytokines may role in the site where the cytokines are syntheses and produced, in neighboring cells and/or in distal cells. The cytokines are significant in the steps of regulation of the cells of the immune system (Zhang, 2007; Dinarello, 2007; Turner et al., 2014). The cytokines are also produced from herniated nucleus pulposus, produced inside the spinal cord of humans (DeLeo et al., 1996), DRG soma (Schafers et al., 2003), or swollen epidermis (Heijmans-Antonissen et al., 2006).

Cytokines in evolution

The cytokines evolved from the molecules before the occurrence of the receptors and signaling cascades. The cytokine-like activities have been shown in all invertebrates like sea animals like fish and the drosophila, where the cytokines played act in tissues of defense and process of repair. Elevate the cytokine-mediated body temperature as a survival method was shown in the lizards (Bernheim and Kluger, 1976). Several cytokine's roles are transcription factors and the extracellular ligands to certain receptors. The biology of cytokine originates from the host formation and production of pus. Most of the cytokines are describing as soluble molecules and factors produced and syntheses by one cell which acts on another cell. Cytokines were known as “lymphokines” to recognize from “monokines” in a try to classify the cytokines by their first sources but which nomenclature was short-lived and then back to “cytokines” (Dinarello, 2007).

The receptors of cytokine

Cytokines do different biological effects via the receptors located on the target cells' membranes. These receptors located on membranes possess an extracellular part. the sequence presence of the amino acid on the extracellular part and these forms inclusive four preserved residues of the cysteine, also the presence of 2 chains of the polypeptide. One of them is a specific subunit called alpha and the other is a subunit called beta subunit. Kinds of the target of cells that bind cytokines are determined by specific receptors located on their membranes. The cytokines and their receptors show similarity for each one and have separation stationary about between10-10 to 10-12 million and that cause of affinity; biological impacts are syntheses and released by types of cytokines and its concentrations measured by picomolar. They show the autocrine activities, the paracrine activities, and the endocrine activities (Wilson et al., 2002). The immune response intensity or duration is regulated and controlled by stimulating and/or stopping the process of activation, the process of proliferation, and the process of differentiation of different cells and controlling the antibodies production. The events of cytokines responses on binding to their receptors include cellular evolution and the humoral response of immune, stimulating of the response of the inflammatory, regulation of hematopoiesis, and control the differentiation of cellular (Owen et al., 2013).

Cytokine types

Interferons

The family of interferon is including a wide group of various types of cytokines. It is inclusive of 3 classes, type I Interferons, type II Interferons, and type III Interferons. The two major type I Interferons Inclusive Interferon-α and Interferon-β. The origin of the interferon term is derived from the cytokine's ability to intervene with the replication of the virus. Type I IFNs show an antiviral activity by inhibiting and prevent viral duplication and replication, elevate the lysis process potential of NKCs, and activating the development of cells called Th1 cells. IFN-γ has a function in the activation of macrophages both in responses of immune (innate and adaptive). The type III IFNs, show the same biological impacts to kind I IFN, playing a significant act in the defense of host cells versus injures that caused by viruses (Abbas et al., 2015; Ank et al., 2006; Parham and Janeway, 2009; Platanias, 2005; Billiau and Matthys, 2009).

Interferon classification and their properties

The interferon is a member of the family of cytokines produced by the host cells to respond to pathogens, bacteria, viruses, etc. Interferons are consisting of 130-170 types of amino acids and the molecular weight of these amino acids is about <100kD and are lysis by the enzymes called proteases, and by chloroform and/or the ketones. The heat stability of interferon is different on the nature of their source (Weiss, 1973). Interferons actions in humans are usually less stable when heated than the other organisms, a decrease in the activity of the interferon is noted after 1 hrs. at 56-60°C (Wheelock, 1965; Freshman et al., 1966). The half-life of type I interferons in humans is about 5-7 hours and is greatly outspread via PE Gylation. The self-crosslinking is associated with stability, the level of action, and biological roles. The investigators have referred that IFNα-2b in humans undergo self-crosslinking to form the stable dimers (Li et al., 2012), and the present system of classification is shown in figure (2). The investigators noted that although the sequence of the amino acid of IFNL4 consists of a binding site to one of the receptor subunits of IFN-III (IL-28Rα), it does not consist of a binding site to IL-10R2, another receptor subunit related with kind III IFNs. The different studies and research demonstrated that stimulates of IFNL4 response and promote antiviral and antibacterial effects via the receptor complex of type III IFN contain the IFNlR1 and the IL-10R2 that making IFNL4 as a member of kind III IFN (Van Boxel-Dezaire et al., 2006; Hamming et al., 2013).

ISSN:0975-3583,0976-2833 VOL12,ISSUE06,2021

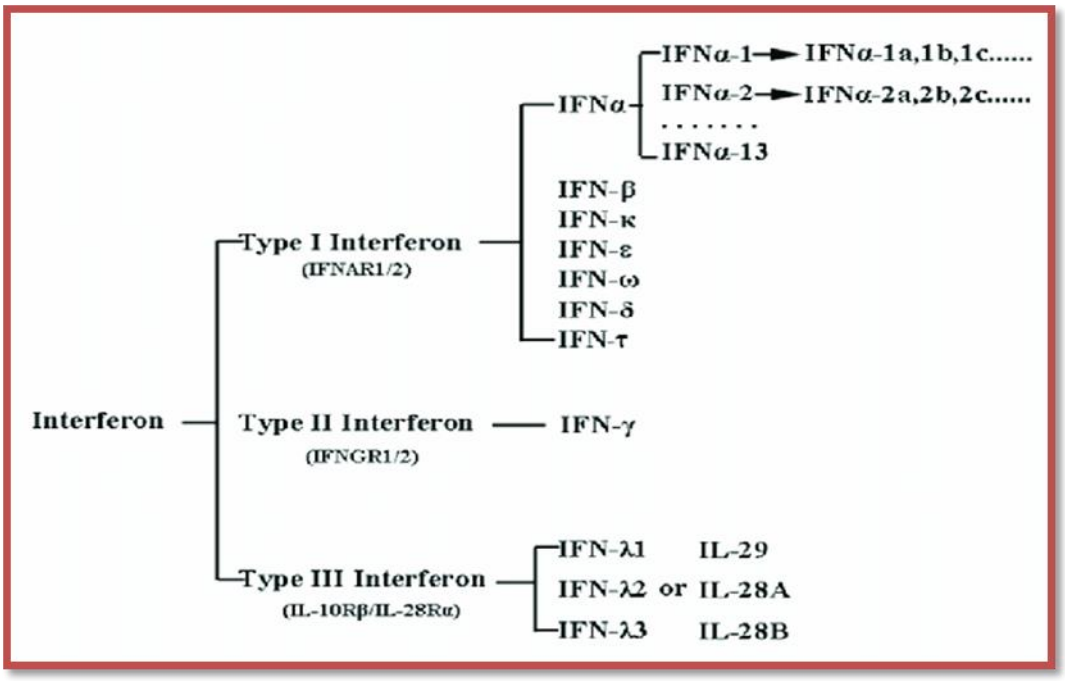

Figure (2): Interferons classification, from (Wang et al., 2017).

Tumor necrosis factor (TNF)

TNF has various biological roles and functions. The cytotoxicity to lines of tumor cells was most one of the first roles to be discovered that causes its name, the tumor necrosis factor (Grell and Scheurich, 2001). TNF-α is syntheses and produced by the cells called monocytes and by the cells called macrophages, and also by different types of cells such as B-and T-cells with fibroblasts that produced fibers of connective tissue (Choy and Panayi, 2001; Butler et al., 1995; Jiang et al., 2017). Structurally, the TNF-α is described as a homo-trimer protein containing about 157 amino acids, mostly generated and produced by the stimulated macrophages, T cells, and NK cells (Horiuchi et al., 2010; Jang et al., 2021). The formation and production of the complexes called IIa and IIb activate caspase-8 and lead to the process of apoptosis. The complex IIc (called necrosome) is composed of RIPK1 and RIPK3 that bind to the form of the complex when they are still un-cleaved. The complex IIc stimulates the mixed lineage kinase domain-like protein (MLKL) through RIPK3-mediated phosphorylation, which leads to necrosis and the process of inflammation (Cho et al., 2009; Holbrook et al., 2019), tumor necrosis factor-alpha signaling pathway is showed in figure (3).

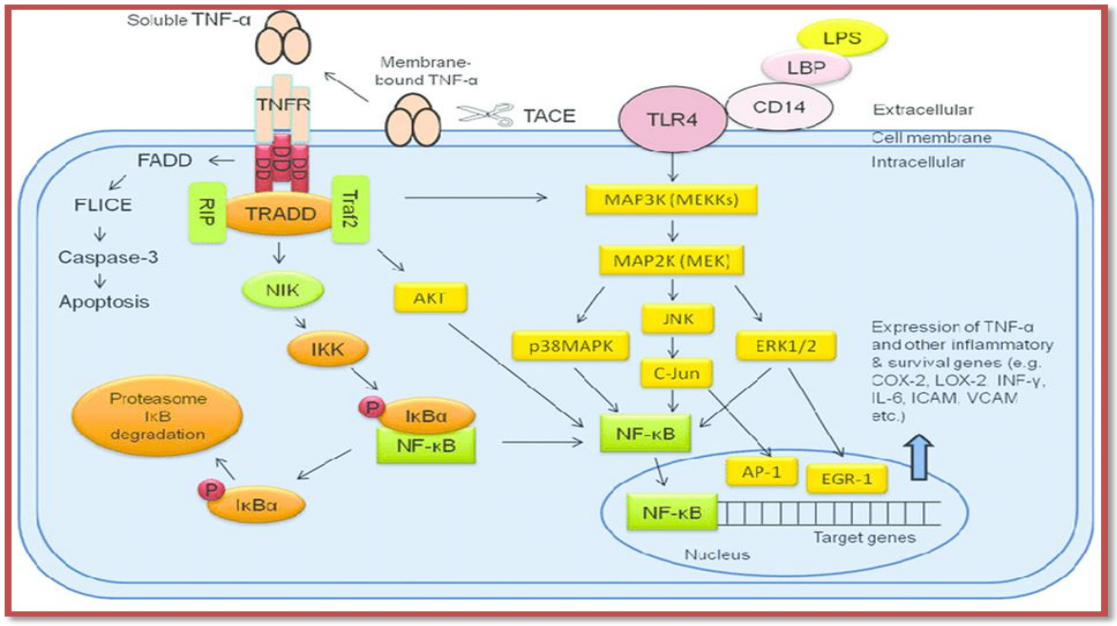

Figure (3): tumor necrosis factor-alpha signaling pathway(Muzamal et al., 2012).

ISSN:0975-3583,0976-2833 VOL12,ISSUE06,2021

TNF is the most common pro-inflammatory cytokine which affects two types of receptors called TNF-R1 and TNF-R2. The TNF-R1 stimulate signaling pathways have been very well described during the last years. Some inflammatory diseases and tumors demonstrate up-regulated levels of the soluble form of TNF-R2 or are related with polymorphisms of TNF-R2, implicating a significant act for TNF-R2 like a therapeutic target (Carpentier et al., 2004; Levin et al., 2016).

Conflict of Interests

The authors of this paper declare that he has no financial or personal relationships with individuals or organizations that would unacceptably bias the content of this paper and therefore declare that there is no conflict of interests.

Source of Funding

The authors have no sources of funding, so it is self-funding research.

Ethical Approve

We declare that the study does not need ethical approval.

References

Abbas AK, Lichtman AH, Pillai S. (2015) Cellular and Molecular Immunology. 8th ed. Philadelphia: Elsevier Saunders; 535 p

Ank N, West H, Bartholdy C, Eriksson K, Thomsen AR, Paludan SR. (2006) Lambda interferon (IFN-lambda), a type III IFN, is induced by viruses and IFNs and displays potent antiviral activity against select virus infections in vivo. Journal of Virology. 80:4501-4509

Barnes P.J. (2008). The cytokine network in asthma and chronic obstructive pulmonary disease. J Clin Invest, 118(11): 3546-3556.

Bernheim HA, Kluger MJ. (1976) Fever and antipyresis in the lizard Dipsosaurus dorsalis. Am J Physiol. 231:198–203.

Billiau A, Matthys P. (2009) Interferon-gamma: A historical perspective. Cytokine & Growth Factor Reviews. 20:97-113.

Butler DM, Maini RN, Feldmann M, Brennan FM (1995) Modulation of proinflammatory cytokine release in rheumatoid synovial membrane cell cultures: comparison of monoclonal anti-TNF-α antibody with interleukin-1 receptor antagonist. Eur Cytokine Netw 6, 225–30.

Carpentier, I.; Beatrice C. and Rudi B. (2004). Function and Regulation of Tumor Necrosis Factor Receptor Type 2. Curr. Med. Chem.11(16):2205-12

Cho, Y.S.; Challa, S.; Moquin, D.; Genga, R.; Ray, T.D.; Guildford, M.; Chan, F.K. (2009) Phosphorylation-driven assembly of the RIP1-RIP3 complex regulates programmed necrosis and virus-induced inflammation. Cell, 137, 1112–1123.

Choy EHS, Panayi GS (2001) Cytokine pathways and joint inflammation in rheumatoid arthritis. NEJM 344, 907–16.

DeLeo JA, Colburn RW, Nichols M, (1996) Interleukin-6-mediated hyperalgesia/allodynia and increased spinal IL-6 expression in a rat mononeuropathy model. J Interferon Cytokine Res, 16:695–700.

Deverman B.E. and Patterson P.H. (2009). Cytokines and CNS development. Neuron 64(1): 61-78.

Dinarello C. A. (2007). Historical Review of Cytokines. Eur J Immunol. 37(Suppl 1): S34–S45.

Dinarello CA. (2007) Historical review of cytokines. European Journal of Immunology, 37: S34-S45

Freshman MM, Merigan TC, Remington JS, Brownlee IE. (1966) In vitro and in vivo antiviral action of an interferon-like substance induced by Toxoplasma gondii. Exp Biol Med. 123: 862-866.

Grell M, Scheurich P (2001) Tumor Necrosis Factors. Encyclopedia of Life Sciences. Nature Publishing Group, Chennai.

Gulati K.; Guhathakurta S.; Joshi J.; Rai N. and Ray A. (2016). Cytokines and their Role in Health and Disease: A Brief Overview. MOJ Immunol 4(2): 00121.

Hamming OJ, Terczyńska-Dyla E, Vieyres G, Dijkman R, Jørgensen SE, et al. (2013) Interferon lambda 4 signals via the IFNλ receptor to regulate antiviral activity against HCV and coronaviruses. EMBO J.; 32: 3055-3065.

Heijmans-Antonissen C, Wesseldijk F, Munnikes RJ, et al. (2006) Multiplex bead array assay for detection of 25 soluble cytokines in blister fluid of patients with complex regional pain syndrome type 1. Mediators Inflamm; 2006:28398.

Holbrook, J.; Lara-Reyna, S.; Jarosz-Griffiths, H.; McDermott, M. (2019) Tumour necrosis factor signaling in health and disease. F1000Research, 8.

Horiuchi, T.; Mitoma, H.; Harashima, S.; Tsukamoto, H.; Shimoda, T. (2010) Transmembrane TNF-alpha: Structure, function, and interaction with anti-TNF agents. Rheumatology, 49, 1215–1228.

Jang, D.-i.; Lee, A-H.; Shin, H.-Y.; Song, H.-R.; Park, J.-H.; Kang, T.-B.; Lee, S.-R.; Yang, S.-H. (2021) The Role of Tumor Necrosis Factor Alpha (TNF-α) in Autoimmune Disease and Current TNF-α Inhibitors in Therapeutics. Int. J. Mol. Sci., 22, 2719.

ISSN:0975-3583,0976-2833 VOL12,ISSUE06,2021

Jiang, Y.; Yu, M.; Hu, X.; Han, L.; Yang, K.; Ba, H.; Zhang, Z.; Yin, B.; Yang, X.P.; Li, Z.; et al. (2017) STAT1 mediates transmembrane TNF-alpha-induced formation of death-inducing signaling complex and apoptotic signaling via TNFR1. Cell Death Differ. 24, 660–671.

Leung, S.; Xuebin L.; Lei F.; Xi C.; Taylor G. and Jingwu Z. (2010). The cytokine milieu in the interplay of pathogenic Th1/Th17 cells and regulatory T cells in autoimmune disease. Cell. Mol. Immuno. 7:182–189.

Levin, A.D.; Wildenberg, M.E.; van den Brink, G.R. (2016) Mechanism of Action of Anti-TNF Therapy in Inflammatory Bowel Disease. J. Crohns Colitis, 10, 989–997.

Li Y, Stafford WF, Hesselberg M, Hayes D, Wu Z, et al. (2012) Characterization of the self-association of human interferon-alpha2b, albinterferon-alpha2b, and Pegasys. J Pharm Sci.; 101: 68-80.

Muzamal I., Robert V.; Henrie A. A. J. and Natali R. M. Phytochemicals as a potential source for TNF-ainhibitors. J. Phytochem Rev. 2012, 12(1): 1-5.

Owen JA, Punt J, Stranford SA (2013) Kuby Immunology. WH Freeman & Company, New York, USA.

Parham P, Janeway C. (2009) The Immune System. 3rd ed. London, New York: Garland Science; 506 p

Platanias LC. (2005) Mechanisms of Type-I- and type-II-interferon-mediated signaling. Nature Reviews Immunology. 5:375-386

Schafers M, Svensson CI, Sommer C, et al. (2003) Tumor necrosis factor-alpha induces mechanical allodynia after spinal nerve ligation by activation of p38 MAPK in primary sensory neurons. J Neurosci; 23:2517–2521.

Turner MD, Nedjai B, Hurst T, Pennington DJ. (2014) Cytokines and chemokines: At the crossroads of cell signaling and inflammatory disease. Biochimica et Biophysica Acta (BBA) – Molecular Cell Research. 1843:2563-2582.

Van Boxel-Dezaire AH, Rani MR, Stark GR. (2006) Complex modulation of cell type-specific signaling in response to type I interferons. Immunity. 25: 361-372

Wang H, Hu H, Zhang K. (2017) Overview of Interferon: Characteristics, signaling and anticancer effect. Arch Biotechnol Biomed. 1: 001-016.

Weiss DL. (1973) Interferons and Interferon Inducers. JAMA.; 226: 570.

Wheelock EF. (1965) Interferon-like virus-inhibitor induced in human leukocytes by phytohemagglutinin. Science. 149: 310-311.

Wilson CJ, Finch CE, Cohen HJ (2002) Cytokines and a cognition-the case for a head-to-toe inflammatory paradigm. J Am Geriatr Soc 50(12): 2041-2056.

Zhang JM, An J. (2007) Cytokines, inflammation, and pain. International Anesthesiology Clinics. 45:27-37

Zídek Z.; Anzenbacher P. and Kmonickoval E. (2009). Current status and challenges of cytokine pharmacology. Br J Pharmacol 157(3): 342- 361.