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Review article

Role of cytokines in the control of inflammation: a review

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ABSTRACT

Cytokines are small secreted proteins released by cells have a specific effect on the interactions and communications between cells. Cytokine is a general name; other names include lymphokine (cytokines made by lymphocytes), monokine (cytokines made by monocytes), chemokine (cytokines with chemotactic activities), and interleukin (cytokines made by one leukocyte and acting on other leukocytes). Cytokines may act on the cells that secrete them (autocrine action), on nearby cells (paracrine action), or in some instances on distant cells (endocrine action). There are both pro-inflammatory cytokines and anti-inflammatory cytokines. There is significant evidence showing that certain cytokines/chemokines are involved in not only the initiation but also the persistence of pathologic pain by directly activating nociceptive sensory neurons. Certain inflammatory cytokines are also involved in nerve-injury/inflammation-induced central sensitization, and are related to the development of contralateral hyperalgesia/allodynia. The discussion presented in this chapter describes several key pro-inflammatory cytokines/chemokines and anti-inflammatory cytokines, their relation with pathological pain in animals and human patients, and possible underlying mechanisms.

Keywords: Cytokines, Proteins, Anti-inflammatory, Chemokine, Cells.

INTRODUCTION

Cytokines are a class of small molecule proteins or polypeptides that are stimulated, synthesized or secreted by immune cells (such as monocytes, macrophages, T cells, B cells, NK cells, etc.) and some non-immune cells (endothelial cells, epidermal cells, fibers mother cells, etc.). Cytokines can transmit information between cells. Cytokines have immune regulation and effector functions including the regulation of innate immunity, adaptive immunity, hematopoiesis, repair of damaged tissues, cell growth, and differentiation. Cytokines play an important role in the immune system by regulating the intensity and duration of immune responses [1].

Types of Cytokines

Cytokines include different types of proteins that direct immune cells, where to go and what to do to keep your immune system functioning correctly [2,3].

Chemokines

Chemokines direct immune cells toward places in your body where they can fight infection.

Interferons

Interferons signal cells to put up their defenses against viruses invading your body. In this way, interferons "interfere" in the process that allows viruses to replicate, or make more viruses once they've invaded a healthy cell.

Interleukins

Interleukins get their name from "inter" which means between and "leukocyte," which is another name for a white blood cell. Originally, scientists thought that leukocytes alone released interleukins and only relayed messages to other leukocytes. But now we know that cells

other than leukocytes release these proteins. Also, interleukins can relay messages between cells that aren't leukocytes.

Tumor necrosis factor (TNF)

TNF helps regulate inflammation in your body. TNF also signals to immune cells that kill tumor cells.

Colony-stimulating factors (CSF)

CSF signals hematopoietic stem cells to develop into specific cell types. Hematopoietic stem cells (HSC) are precursor cells that give rise to all blood cell types: white blood cells, red blood cells and platelets. These changes take place during a process called hematopoiesis. For example, granulocyte-colony stimulating factor (G-CSF) signals an HSC to become a white blood cell called a neutrophil. Neutrophils help fight infection.

Some cytokines get their names from the type of cell that makes them, including:

Lymphokines

Produced by lymphocytes, a type of white blood cell.

Monokines

Produced by monocytes, a type of white blood cell.

Nomenclature of the cytokines

Nomenclature has been a problem because these molecules were originally named after the activity that they described, or cell types they derived from. This results in a large number of 3 or 4 letter acronyms. Names such as interleukines, chemokines, monokines, interferons, colony-growth factors are the general terms to describe cytokines fallen into different categories. Cytokines are small secreted proteins that mediate and regulate immunity, inflammation, and hematopoiesis. However, it has been shown that membrane bound forms of cytokines, such as membrane bound TNF alpha (mTNF), also exhibit biological activities. Cytokines are produced de novo in response to an immune stimulus. They generally (although not always) act over short distances and short time spans and at very low concentration. They act by binding to specific cell surface receptors, which then signal the cell via kinase cascades, often tyrosine kinases, to modulate gene expression. The gene products (proteins) participate in the cell proliferation, differentiation, migration, and apoptosis activities.

Properties of Cytokines

Pleiotropy affects multiple cell types Redundancy Multiple cytokines affects cells of the same type Synergy Cytokines acting in concert on the same cell Antagonism Competing actions Cascading Cytokines acting sequentially

Mechanisms underlying cytokines-mediated pathological pain

There is evidence that pro-inflammatory cytokines (e.g., IL-1β, TNF-α) [4, 5, 6] and chemokines (e.g., MCP-1) [7,9] may directly modulate neuronal activity in various classes of neurons in the peripheral and central nervous system. In the peripheral nervous system, abnormal spontaneous activity can be evoked from nociceptive neurons by topical application of TNF-α to the peripheral axons *in vivo* [10], or to the somata of the DRG neurons *in vitro* [11]. Large, myelinated fast conducting Aβ neurons can also be excited by topical application of TNF-α to the DRG [12] or by an autologous HNP extract [13]. TNF-α can enhance the sensitivity of sensory neurons to the excitation produced by capsaicin and this enhancement likely is mediated by the neuronal production of prostaglandins [14, 15, 16]. It was found that TNF-α-induced neuronal excitation is mediated by cAMP-dependent protein kinase (PKA) pathway [17, 18, and 19]. The p38 mitogen-activated protein kinase (MAPK) is also involved in TNF-α-induced cutaneous hypersensitivity to mechanical or thermal stimulation [20, 21]. Results obtained from IL-6 knockout mice indicates that IL-6 plays a facilitating role in sympathetic sprouting induced by nerve injury and that its effect on pain behavior is indirectly mediated through sympathetic sprouting in the DRG [22]. Most recently, it is reported that localized inflammation of the DRG up-regulates a number of pro-inflammatory cytokines including IL-6 and induces abnormal sympathetic sprouting in the absence of peripheral nerve injury [23, 24]. It suggests a possible correlation between inflammatory responses and sympathetic sprouting, which are two well-known mechanisms implicated in various chronic pain states. In summary, proinflammatory cytokines are involved in the development of inflammatory and neuropathic pain. Just as specific cytokines and their neutralizing antibodies have been introduced into clinical trials for the treatment of stroke, Alzheimer's disease, autoimmune diseases, wound healing, and amyotrophic lateral sclerosis, one could utilize local or systemic delivery of anti-inflammatory cytokines or inflammatory cytokine antagonists for the treatment of chronic pain. These specific cytokines or antagonists would act to disrupt the hyperexcitability cycle taking place in the

sensory neurons, providing a new, non-opioid therapeutic approach for the treatment of pathological pain due to inflammation or peripheral nerve injury.

CONCLUSIONS

Cytokine is a highly active field of study and can provide comprehensive insights for disease diagnosis and treatment. The current techniques have successfully demonstrated their potential to provide highly sensitive and time-efficient detection with various signal readouts either for in vitro or in vivo applications. In this review, we summarized various cytokine functions in immune and inflammatory responses and reviewed the stability of cytokines under different processing and storage conditions which is critical for accurate and reliable cytokine quantification.

REFERENCES

1. Zhang JM, a J, 2007. Cytokines, Inflammation and Pain. International Anesthesiology Clinics. 45(2), Pages- 27–37. Doi: 10.1097/AIA.0b013e318034194e.

2. Sweitzer S, Deleo JA, Martin D,1999. Intrathecal interleukin-1 receptor antagonist and tumor necrosis factor binding protein exhibit an antiallodynic effect in a rat model of neuropathic pain. Society for Neuroscience. 25(2), pages 5794-5798. Doi: https://doi.org/10.1016/S0306-4522 (00)00574-1.

3. White FA, Sun J, Waters SM, et al, 2005, Excitatory monocyte chemoattractant protein-1 signaling is up-regulated in sensory neurons after chronic compression of the dorsal root ganglion. Proceedings of the National Academy of Sciences of the United States of America. 102(4), pages 14092–14097. Doi: 10.1073/pnas. 0503494102.

4. Berman JW, Guida MP, Warren J, et al, 1996. Localization of monocyte chemoattractant peptide-1 expression in the central nervous system in experimental autoimmune encephalomyelitis and trauma in the rat. Journal of Immunology. 156(2), Pages 3017–3023. Doi: 10.1007/978-3-642-84861-849.

5. Taskinen HS, Roytta M, 2000. Increased expression of chemokines (MCP-1, MIP-1alpha, RANTES) after peripheral nerve transection. Journal of the Peripheral Nervous System. 5(4), Pages 75–81. Doi: 10.1046/j.1529-8027.2000.00008.x.

6. Oh SB, Tran PB, Gillard SE, et al, 2001. Chemokines and glycoprotein120 produce pain hypersensitivity by directly exciting primary nociceptive neurons. The Journal of Neuroscience. 21(2), Pages 5027–5035. Doi: 10.1523/JNEUROSCI.21-14-05027.2001.

7. Abbadie C, Lindia JA, Cumiskey AM, et al, 2003. Impaired neuropathic pain responses in mice lacking the chemokine receptor CCR2. Proceedings of the National Academy of Sciences of the United States of America. 100(4), pages 7947–7952. Doi: 10.1073/pnas. 1331358100.

8. Wieseler-Frank J, Maier SF, Watkins LR,2004. Glial activation and pathological pain. Neurochemistry International. 45(2), Pages 389–395. Doi: 10.1016/j. neuint.2003.11.010.

9. Milligan ED, Sloane EM, Langer SJ, et al, 2005. Controlling neuropathic pain by adeno-associated virus driven production of the anti-inflammatory cytokine, interleukin-10. Molecular Pain 1. Page 9-12. Doi: 10.1186/1744-8069-1-9.

10. Uceyler N, Valenza R, Stock M, et al, 2006. Reduced levels of anti-inflammatory cytokines in patients with chronic widespread pain. Arthritis and Rheumatism. 54(4), Pages 2656–2664. Doi: 10.1002/art.22032.

11. Unsicker K, Flanders KC, Cissel DS, et al,1991. Transforming growth factor beta isoforms in the adult rat central and peripheral nervous system. Neuroscience. 44(3), Pages 613–625. Doi: 10.1016/0306-4522(91)90086-N.

12. Roberts AB, Sporn MB, 1993. Physiological actions and clinical applications of transforming growth factor-beta (TGF-beta). Growth Factors. 8(2), Pages 1–9. Doi: 10.3109/08977199309028968.

13. Kiefer R, Lindholm D, Kreutzberg GW, 1993. Interleukin-6 and transforming growth factor-beta 1 mRNAs are induced in rat facial nucleus following motoneuron axotomy. European Journal of Neuroscience. 5(2), Pages 775–781. Doi: 10.1111/j.1460-9568.1993.tb00204.x.

14. Meller ST, Gebhart GF, 1993. Nitric oxide (NO) and nociceptive processing in the spinal cord. Pain. 52(4), Pages 127–136. Doi: 10.1016/0304-3959(93)9017 9-P.

15. Chapman GA, Moores K, Harrison D, et al, 2000. Fractalkine cleavage from neuronal membranes represents an acute event in the inflammatory response to excitotoxic brain damage. The Journal of Neuroscience. 20(4), Pages 87-97. Doi: 10.1523/JNEUROSCI.2 0-15-j0002.2000.

16. Winkelstein BA, Rutkowski MD, Sweitzer SM, et al, 2001. Nerve injury proximal or distal to the DRG induces similar spinal glial activation and selective cytokine expression but differential behavioral responses to pharmacologic treatment. Journal of Comparative Neurology. 439(2), Pages 127–139. Doi: 10. 1002/cne.1340.

17. Watkins LR, Maier SF, 2002. Beyond neurons: Evidence that immune and glial cells contribute to pathological pain states. Physiological Reviews. 82(3), Pages 981–1011. Doi: 10.1152/physrev.00011.2002.

18. DeLeo JA, Rutkowski MD, Stalder AK, et al, 2000. Transgenic expression of TNF by astrocytes increases mechanical allodynia in a mouse neuropathy model. Neuroreport. 11(2), Pages 599–602. Doi: 10.1097/00001 756-200002280-00049.

19. Milligan ED, Twining C, Chacur M, et al, 2003. Spinal glia and proinflammatory cytokines mediate mirror-image neuropathic pain in rats. The Journal of Neuroscience. 23(3), Pages 1026–1040. Doi: 10.1523/JNE UROSCI.23-03-01026.2003.

20. Wu DC, Jackson-Lewis V, Vila M, et al, 2002. Blockade of microglial activation is neuroprotective in the 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine mouse model of Parkinson disease. The Journal of Neuroscience. 22(2), Pages 1763–1771. Doi: 10.1523/JNE UROSCI.22-05-01763.2002.

21. Lu X, Richardson PM, 1991. Inflammation near the nerve cell body enhances axonal regeneration. The Journal of Neuroscience. 11(4), Pages 972–978. Doi: 10.1523/JNEUROSCI.11-04-00972.1991.

22. Leech RW, 1967. Changes in satellite cells of rat dorsal root ganglia during central chromatolysis. An electron microscopic study. Neurology. 17(2), Pages 349–358. Doi: 10.1212/WNL.17.4.349.

23. Woodham P, Anderson PN, Nadim W, et al, 1989. Satellite cells surrounding axotomised rat dorsal root ganglion cells increase expression of a GFAP-like protein. Neuroscience Letters. 98(2), Pages 8–12. Doi: 10.1016/0304-3940(89)90495-8.

24. Zhang JM, Li HQ, Liu B, et al,2002. Acute topical application of tumor necrosis factor alpha evokes protein kinase A-dependent responses in rat sensory neurons. Journal of Neurophysiology. 88(6), Pages 1387–1392. Doi: 10.1152/jn.2002.88.3.1387.