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Immunomodulators in Autoimmunity and Viral Infections

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Abstract

Immunologically-based therapies are steadily moving from the laboratory to clinical practice. In that regard, the elevated levels of "immunocytokine" gene expression, including, tumor necrosis factor-α, various interleukins, cytotoxic T-cell antigen-4, B-cell activating factor, and others, are characteristic of autoimmune diseases, such as rheumatoid arthritis, inflammatory bowel diseases, psoriatic arthritis and system lupus erythematosus and, some cancers as well. Treatment of these autoimmune diseases with first-line Immunologically-based therapies can ameliorate the pathology associated with autoimmunity and cancer and, can also inhibit transplant rejection. Importantly, drugs containing immunomodulatory activity are now also known to have significant and effective anti-viral activity which may result from their role in reducing the impact of "immunocytokines" on viral infectivity and disease progression. Although vaccine development continues to alter the landscape of virally-associated diseases, immunomodulation has become a useful paradigm for reducing the pathology associated with viral infection(s) going forward.

Keywords: Immunocytokine; Inflammatory bowel disease; Autoimmune disease; Host response

Introduction

Many drugs are immunomodulatory because they have significant clinical efficacy in the therapy of autoimmune diseases, cancer, infection and transplantation [1-3]. For example, methotrexate (MTX), cyclosporine and tracrolimus are three immunomodulatory drugs which are commonly employed in the first-line therapy of rheumatoid arthritis (RA) [4-6] and various forms of irritable bowel disease (IBD) [7] because of their potent effects on suppressing immune mechanisms that contribute to the progression of these diseases. In that regard, MTX has also recently been classified as an inhibitor of Janus kinase/Signal Transducers and Activators of Transcription (JAK/STAT) signaling [8], the activation of which contributes to the significant up-regulation of pro-inflammatory cytokine gene expression [9-11] as well as aberrant cell survival [12,13] which are both associated with RA and IBD.

Immunomodulation has also been a focus for altering host responses in the therapy of viral and other forms of infection. Thus, interferon-α (INF-α) and IFN-β, commonly referred to as the type I interferons are the major effector cytokines orchestrating the host's response to viral [14,15] and bacterial infections [16,17]. In several of these cases, the immunomodulatory function(s) of effective agents can be traced back to their capacity to block various inhibitory signals that impair immune cell function, including, cytotoxic T-lymphocyte-associated protein, (CTLA-4), also known as CD152, programmed cell death-1 (PD-1) protein and B-and T-lymphocyte attenuator (BTLA) protein, [1], as well as additional various targets on tissue-resident memory T-lymphocytes [18], the latter cell type having been shown to be an important immune cell target for inducing immunomodulation. More recently, the immunomodulatory activity of mesenchymal stem cells (MSCs) have also become increasingly appreciated [19,20].

Of particular interest in the context of future cancer therapies [21], and perhaps even autoimmune diseases, is the role played by PD-1 as a regulator of T-cell immune function. PD-1 is a member of the CD28 superfamily of proteins that convey negative signaling after PD-1 interacts with 2 of its ligands, namely, PD-L1 or PD-L2. In that regard, the PD-1 signaling pathway is known to modify the induction and maintenance of peripheral tolerance which if "broken" can result in autoimmune disease [21], various types of cancer [22-24] and infections [23]. Thus, monoclonal antibodies which block PD-1-mediated signaling have been shown to produce a measurable and sustainable clinical response in a subset of patients diagnosed with breast or ovarian cancers [24], especially in those patients with PD-L1-positive cells. Importantly, immunomodulation of PD-L1-positive cancer cells could result in the long sought-after specific therapy of these cancers.

"Immunocytokines": Role in Autoimmunity and Infection

The conceptual framework underpinning immunomodulation [25] has moved forward by employing a strategy for the development of clinical therapies for various adult and pediatric immune-mediated diseases, cancer, as well as viral and bacterial infections [26-39]. Noteworthy also is the recent attention paid to the D3 metabolite of vitamin D [35,40], antibiotics [41], probiotics [42], and long chain omega-3 fatty acids [43] therefore adding to the list of potential immunomodulating agents.

As expected to be the case that is based on the underlying pathogenesis of autoimmune diseases, cancer and viral infections, "immunocytokines" have become one of the most critical targets for inducing immunomodulation in autoimmune diseases and viral infections [44]. Among these targeted "immunocytokines" are the more classical anti-cytokine targets such as TNF-α [45] IL-6 [46], IL-1ß [47], cytotoxic T-lymphocyte antigen-4 (CTLA-4) [48], B-cell

activating factor (BAFF) [49], nuclear factor κ-B ligand (RANKL) [50], and INF-γ [51,52]. However, more recently, complement receptors [53,54], IL-9 [55,56], IL-12 [57], IL-23 [58] IL-17 [59], IL-23 [60], IL-33/ST2 [61] and IL-35 [62] have been added to the list of potential targets for immunomodulation (Table 1). In that regard, drug development is underway to explore how intervening in the activity of these factors might alter host immune responses. Even immune checkpoint inhibitors, in addition to CTLA-4-Ig [49], are in development although their long-term clinical efficacy and potential adverse effects have yet to be established [63]. What does appear to be the case is that all of these molecules have been established as potential targets through basic and pre-clinical research which ascribed important roles to them in these various autoimmune, cancer and viral conditions. The results of these studies indicated that autoimmune diseases, cancer and viral infections were modifiable through immunomodulation which should result in improved clinical responses.

Cytokine	Function(s)	References
TNF-α	↑Apoptosis; Gene Expression↔	45, 46
IL-6	↑Apoptosis; Gene Expression↔	46
IL-1β	↑Apoptosis; Gene Expression↔	47
CTLA-4	T-cell activation; Checkpoint	48
BAFF	B-cell activation	49
RANKL	Osteoclast Development	50
INF-γ	Anti-proliferation; Intracellular Signaling	51, 52
C3aR, C5aR, CD21	T-cell activation; C3d binding	53, 54
IL-9	Co-stimulatory with TGF-β, IL-4	55, 56
IL-12	Anti-microbial; Anti-cancer	57
IL-23	Regulation of TH1 and TH17	58
IL-17	Expressing RORγt+CD4+ T cell	59
IL-23	Regulation of memory T-cells	60
IL-33/ST2	Enhancement of natural killer, Th1, and CD4 and CD8 T-cell functions	61
IL-35	Immunosuppression of Treg and B-cells	62

Table 1: Immunocytokines: Influence on Immunomodulatory Functions.

Is there a connection between "Immunocytokine" activity and viral infections?

Compelling evidence now links the elevated production of "immunocytokines" characteristic of autoimmune diseases with the pathogenesis and progression of viral infections [61]. This link includes an association between "immunocytokines" and influenza [64,65], hepatitis C [66,67], enterovirus [68] and HIV-1 [69], to name only a few. At the cellular level Jenabian et al. [70] showed that T-regulatory (Treg) cells whose function is compromised in RA, can also affect the development of anti-HIV responses as evidenced by the finding that Treg cells could suppress anti-HIV-specific immune responses and may even alter the rate of HIV-1 progression to full-blown acquired immune deficiency syndrome. This is likely to occur as a result of enhanced cytokine production as a component of Treg cell function, although the continued attention paid to the possibility that Treg cells may also cause adverse events in persons infected with HIV-1 as a result of hyperimmune activation must also be considered.

In addition to the apparent link between the elevated production of "immunocytokines" and viral infection, increased vigilance must be paid to the possibility that immunomodulation of the progression of RA with drugs such as MTX or leflunomide may also have distinct deleterious effects if patients with active RA also become virally-infected, although no evidence supported a connection between the therapy of RA with MTX and varicella herpes zoster [71]. On the other hand, the anti-viral activity associated with leflunomide [72] did not protect patients from various secondary skin infections. Finally, the presence of anti-cyclic citrullinated peptide (anti-CCP) antibodies, in certain individuals which have been recently touted as a powerful biomarker and positive predictor for the later development of RA [73] are also associated with the development of some viral infections, such as tuberculosis, but anti-CCP antibodies were rarely seen in patients with hepatitis infection [74].

The current status of employing immunomodulation to treat viral infections

Direct therapy of viral infections is a daunting medical problem that is compounded by the fact that one must know the extent to which modification or targeting non-specific or specific innate or adaptive immune responses will result in a clinical response to the virus. Because vaccine development is a slow and laborious proposition, immunotherapy has become a potential suitable alternative for treating viral infections [75-78]. For example, some of the appropriate targets for immunomodulation of severe influenza proposed by Darwish et al. [77] were TNF blockade, statins, glucocorticoids, cyclooxygenase-2 (COX-2), macrolides, peroxisome proliferator-activated receptor agonists, AMP-activated protein kinase agonists and high mobility group (HMG) box 1 antagonists. Interestingly, some of these targets, in particular, TNF-α, COX-2, HMG, are also critical factors for sustaining chronic inflammation associated with autoimmune diseases [79]. In fact, the TNF receptor has been considered a potential adjuvant for viral vaccines based on the role played by CD8+ lymphocytes during viral infection [80]. Another target that appears to have clinical utility for treating viral infections such as hepatitis C is INF-α combined ribovarin with or without ribovarin [81,82]. In that context, changes in the level of interferon-stimulated CXCL10 was considered a useful measurement for assessing residual clinical activity associated with hepatitis C infection [82]. An anti-INF-α strategy has also been considered possible for immunomodulating HIV-1 infection [83]. Of note, according to Pulliam [83] the INF-α strategy might also have utility for identifying HIV-1-infected individuals with associated immune activation and resultant cognitive abnormalities. A few more recent approaches for immunomodulation of viral infections include, strategies for ramping up the activity of natural killer cells [84], developing what has been termed a, "killer peptide" to seek out and kill viral and other microbial-based infectious organisms [85], employing "decoy" receptors that do have host counterparts [86], and poxviral proteins, such as is found in variola (smallpox) virus which are formed

from genetic sequences that alter the function of immunomodulatory proteins that bind cytokines [87].

Conclusions and Future Perspectives

At the present time, there is every indication that "immunocytokines" drive the pathogenesis and progression of autoimmune diseases. However, "immunocytokines" are also significantly involved in the host's response to viral infections. Therefore experimentally-based strategies designed to harness the power of immunomodulation which has been foremost in the development of biologic drugs for treating RA, IBD, including Crohn's disease; psoriatic arthritis, ankylosing spondylitis and lupus also appear to have a strong rationale for current and future development of anti-viral drugs. Vaccine development for autoimmune diseases, such as RA, [88] is a lengthy and costly venture. This makes the exploitation of recent discoveries in the field of immunomodulation an alternative strategy worth considering for treating viral illnesses.

References

1. Wu YL, Liang J, Zhang W, Tanaka Y, Sugiyama H (2012) Immunotherapies: the blockade of inhibitory signals. Int J Biol Sci 8: 1420-1430.
2. Tas SW, Baeten DL (2016) Recent advances in the treatment of immune-mediated inflammatory diseases. Methods Mol Biol 1371: 143-155.
3. Lele AC, Mishra DA, Kamil TK, Bhakta S, Degani MS (2016) Repositioning of DHFR inhibitors. Curr Top Med Chem 16: 2125-2143.
4. Nogueira E, Gomes A, Preto A, Cavaco-Paulo A (2016) Update on therapeutic approaches for rheumatoid arthritis. Curr Med Chem 23: 2190-2202.
5. Subesinghe S, Scott IC (2015) Key findings from studies of methotrexate tapering and withdrawal in rheumatoid arthritis. Expert Rev Clin Pharmacol 8: 751-760.
6. Kitahara K, Kawai S (2007) Cyclosporine and tacrolimus for the treatment of rheumatoid arthritis. Curr Opin Rheumatol 19: 238-245.
7. Ahluwalia JP (2012) Immunotherapy in inflammatory bowel disease. Med Clin North Amer 96: 525-544.
8. Thomas S, Fisher KH, Snowden JA, Danson SJ, Brown S, et al. (2015) Methotrexate is a JAK/STAT inhibitor. PLoS One 10: e0130078.
9. Miossec P (2004) An update on the cytokine network in rheumatoid arthritis. Curr Opin Rheumatol 16: 218-222.
10. Asquith DL, McInnes IB (2007) Emerging cytokine targets in rheumatoid arthritis. Curr Opin Rheumatol 19: 246-251.
11. Mateen S, Zafar A, Moin S, Khan AQ, Zubair S (2016) Understanding the role of cytokines in the pathogenesis of rheumatoid arthritis. Clin Chim Acta 455: 161-171.
12. Ivashkiv LB, Hu X (2004) Signaling by STATs. Arthritis Res Ther 6: 159-168.
13. Malemud CJ (2013) Intracellular signaling pathways in rheumatoid arthritis. J Clin Cell Immunol 4: 160.
14. Meyer O (2009) Interferons and autoimmune disorders. Joint Bone Spine 76: 464-473.
15. González-Navajas JM, Lee J, David M, Raz E (2012) Immunomodulatory functions of type I interferons. Nat Rev Immunol 12: 125-135.
16. Labro MT (2012) Immunomodulatory effects of antimicrobial agents. Part i: antibacterial and antiviral agents. Expert Rev Anti Infect Ther 10: 319-340.
17. Kak V, Sundareshan V, Modi J, Khadori NM (2012) Immunotherapies in infectious diseases. Med Clin North Amer 96: 455-474.
18. Shin H, Iwasaki A (2013) Tissue-resident memory T cells. Immunol Rev 255: 165-181.
19. Najar M, Raicevic G, Fayyad-Kazan H, Bron D, Toungouz M, et al. (2016) Mesenchymal stromal cells and immunomodulation: A gathering of regulatory immune cells. Cytotherapy 18: 160-171.
20. Wolff Z, Malemud CJ (2016) Controversies in the use of mesenchymal stem cells for treating autoimmune diseases: Mesenchymal Stem Cells and Immunomodulation. Springer.
21. Jin HT, Ahmed R, Okazaki T (2011) Role of PD-1 in regulating T-cell immunity. Curr Top Microbiol Immunol 350: 17-37.
22. Medina PJ, Adams VR (2016) PD-1 pathway inhibitors. Immuno-oncology agents for restoring antitumor immune responses. Pharmacotherapy 36: 317-334.
23. Chikuma S (2016) Basics of PD-1 in self-tolerance, infection, and cancer immunity. Int J Clin Oncol 21: 448-455.
24. Emens LA, Kok M, Ojalvo LS (2016) Targeting the programmed cell death-1 pathway in breast and ovarian cancer. Curr Opin Obstet Gynecol 28: 142-147.
25. Martin-Liberal J, Ochoa de Olza M, Hierro C, Gros A, Rodon J, et al. (2017) The expanding role of immunotherapy. Cancer Treat Rev 54: 74-87.
26. Hou JK, Velayos F, Terrault N, Mahadevan U (2010) Viral hepatitis and inflammatory bowel disease. Inflamm Bowel Dis 16: 925-932.
27. Silva SC, Ortigosa LC, Benard G (2010) Anti-TNF-α agents in the treatment of immune-mediated inflammatory diseases: mechanisms of action and pitfalls. Immunotherapy 2: 817-833.
28. Dreyfus DH (2011) Autoimmune disease: a role for new anti-viral therapies? Autoimmun Rev 11: 88-97.
29. O'Shea JJ, Kontzias A, Yamaoka K, Tanaka Y, Laurence A (2013) Janus kinase inhibitors in autoimmune diseases. Ann Rheum Dis 72 Suppl 2: 111-115.
30. Nuti F, Civitelli F, Cucchiara S (2014) Long-term safety of immunomodulators in pediatric inflammatory diseases. Paediatr Drugs 16: 343-352.
31. Chen J, Wu M, Wang J, Li X (2015) Immunoregulation of NKT cells in systemic lupus erythematosus. J Immunol Res 2015: 206731.
32. Ward MG, Irving PM, Sparrow MP (2015) How should immunomodulators be optimized when used as combination therapy with anti-tumor necrosis factor agents in the management of inflammatory bowel disease? World J Gastroenterol 21: 11331-11342.
33. Genovese MC, Kremer J, Zamani O, Ludivico C, Krogulec M, et al. (2016) Baricitinib in patients with refractory rheumatoid arthritis. N Engl J Med 374: 1243-1252.
34. Maddocks K, Jones JA (2016) Bruton tyrosine kinase in chronic lymphocytic leukemia. Semin Oncol 43: 251-259.
35. Durcan L, Petri M (2016) Immunomodulators in SLE: Clinical evidence and immunologic actions. J Autoimmun 74: 73-84.
36. Sharara AI (2016) When to start immunomodulators in inflammatory bowel disease? Dig Dis 34: 125-131.
37. Khalil DN, Smith EL, Brentjens RJ, Wolchok JD (2016) The future of cancer treatment: immunomodulation, CARs and combination immunotherapy. Nat Rev Clin Oncol 13: 273-290.
38. Allen PB, Peyrin-Biroulet L (2016) Immunomodulators for the treatment of Crohn's disease in adults: optimal use and prospects for future drug treatments. Expert Rev Clin Immunol 12: 741-749.
39. Jelinek T, Kufova Z, Hajek R (2016) Immunomodulatory drugs in AL amyloidosis. Crit Rev Oncol Hematol 99: 249-260.
40. Szymczak I, Pawliczak R (2016) The active metabolite of vitamin D3 as a potential immunomodulator. Scand J Immunol 83: 83-91.
41. Zapater P, González-Navajas JM, Such J, Francés R (2015) Immunomodulating effects of antibiotics used in the prophylaxis of bacterial infections in advanced cirrhosis. World J Gastroenterol 21: 11493-11501.
42. Kang HJ, Im SH (2015) Probiotics as an immune modulator. J Nutr Sci Vitaminol (Tokyo) 61 Suppl: 103-105.

43. Fenton JI, Hord NG, Ghosh S, Gurzelli EA (2013) Immunomodulation by dietary long chain omega-3 fatty acids and the potential for adverse health outcomes. Prostaglandins Leukot Essent Fatty Acids 89: 379-390.
44. Bootz F, Neri D (2016) Immunocytokines: a novel class of products for the treatment of chronic inflammation and autoimmune conditions. Drug Discov Today 21: 180-189.
45. Feldmann M, Brennan FM, Maini RN (1996) Rheumatoid arthritis. Cell 85: 307-310.
46. Malemud CJ, Blumenthal DE (2014) Protein kinase small molecule inhibitors for rheumatoid arthritis: Medicinal chemistry/Clinical perspectives. World J Orthop 5: 496-503.
47. Geyer M, Müller-Ladner U (2010) Actual status of antiinterleukin-1 therapies in rheumatic diseases. Curr Opin Rheumatol 22: 246-251.
48. Walker LS (2017) EFIS Lecture: Understanding the CTLA-4 checkpoint in the maintenance of immune homeostasis. Immunol Lett 184: 43-50.
49. Basha S, Pichichero ME (2017) Decreased TNF family receptor expression on B-cells is associated with reduced humoral responses to Streptococcus pneumoniae infections in young children. Cell Immunol 320: 11-19.
50. Croft M, Siegel RM (2017) Beyond TNF: TNF superfamily cytokines as targets for the treatment of rheumatic diseases. Nat Rev Rheumatol 13: 217-233.
51. Kötter I, Hamuryudan V, Oztürk ZE, Yazici H (2010) Interferon therapy in rheumatic diseases: state-of-the-art 2010. Curr Opin Rheumatol 22: 278-283.
52. Kotenko SV (2011) IFN-γs. Curr Opin Immunol 23: 583-590.
53. Strainic MG, Shevach EM, An F, Lin F, Medof ME (2013) Absence of signaling into CD4+ cells via C3aR and C5aR enables autoinductive TGF-ß1 signaling and induction of Foxp3+ regulatory T cells. Nat Immunol 14: 162-171.
54. Hannan P (2016) The structure-function relationships of complement receptor type 2 (CR2; CD21). Curr Protein Pept Sci 17: 463-487.
55. Deng Y, Wang Z, Chang C, Lu L, Lau CS, et al. (2017) Th9 cells and IL-9 in autoimmune disorders: Pathogenesis and therapeutic potentials. Hum Immunol 78: 120-128.
56. Rivera Vargas T, Humblin E, Végran F, Ghiringhelli F, Apetoh L (2017) TH9 cells and anti-tumor immunity. Semin Immunopathol 39: 39-46.
57. Behzadi P, Behzadi E, Ranjbar R (2016) IL-12 family cytokines: General characteristics, pathogenic microorganisms, receptors, and signalling pathways. Acta Microbiol Immunol Hung 63: 1-25.
58. Braun J (2016) New targets in psoriatic arthritis. Rheumatology (Oxford) 55: 30-37.
59. Kim BS, Park YJ, Chung Y (2016) Targeting IL-17 in autoimmunity and inflammation. Arch Pharm Res 39: 1537-1547.
60. Li Y, Wang H, Lu H, Hua S (2016) Regulation of memory T cells by interleukin-23. Int Arch Allergy Immunol 169: 157-162.
61. Mehraj V, Ponte R, Routy JP (2016) The dynamic role of the IL-33/ST2 axis in chronic viral infections: Alarming and adjuvanting the immune response. EBioMedicine 9: 37-44.
62. Choi J, Leung PS, Bowlus C, Gershwin ME (2015) IL-35 and autoimmunity: A comprehensive perspective. Clin Rev Allergy and Immunol 49: 327-332.
63. Day D, Hansen AR (2016) Immune-related adverse events associated with immune checkpoint inhibitors. BioDrugs 30: 571-584.
64. Toplak N, Avcin T (2009) Influenza and immunity. Ann NY Acad Sci 1173: 619-626.
65. Liu Q, Zhou YH, Yang ZQ (2016) The cytokine storm of severe influenza and development of immunomodulatory therapy. Cell Mol Immunol 13: 3-10.
66. Fallahi P, Ferri C, Ferrari SM, Corrado A, Sansonno D, et al. (2012) Cytokines and HCV-related disorders. Clin Dev Immunol 2012: 468107.
67. Alao H, Jake Liang T (2014) Alternative interferons and immunomodulators in the treatment of hepatitis C. Liver Int 34 Suppl 1: 133-138.
68. Wang SM, Lei HY, Liu CC (2012) Cytokine immunopathogenesis of enterovirus 71 brain stem encephalitis. Clin Dev Immunol 2012: 876241.
69. Shankar EM, Velu V, Vignesh R, Vijayaraghavalu S, Rukumani DV, et al. Recent advances targeting innate immunity-mediated therapies against HIV-1 infection. Microbiol Immunol 56: 497-505.
70. Janabian MA, Ancuta P, Gilmore N, Routy JP (2012) Regulatory T cells in HIV infection: can immunotherapy regulate the regulator? Clin Dev Immunol 2012: 908314.
71. Zhang N, Wilkinson S, Riaz M, Östör AJ, Nisar MK (2012) Does methotrexate increase the risk of varicella or herpes zoster infection in patients with rheumatoid arthritis? A systematic literature review. Clin Exp Rheumatol 30: 962-971.
72. Smith KJ, Germain M (2015) Leflunomide: an immune modulating drug that may have a role in controlling secondary infections with a review of its mechanisms of action. J Drugs Dermatol 14: 230-236.
73. Sakkas LI, Bogdanos DP, Katsiari C, Platsoucas CD (2014) Anti-citrullinated peptides as autoantigens in rheumatoid arthritis-relevance to treatment. Autoimmun Rev 13: 1114-1120.
74. Lima I, Santiago M (2010) Antibodies against cyclic citrullinated peptides in infectious diseases—a systematic review. Clin Rheumatol 29: 1345-1351.
75. Hegde NR, Rao PP, Bayry J, Kaveri SV (2009) Immunotherapy of viral infections. Immunotherapy 1: 691-711.
76. Rijckborst V, Sonneveld MJ, Janssen HL (2011) Chronic hepatitis B – anti-viral or immunomodulatory therapy? Aliment Pharmacol Ther 33: 501-513.
77. Darwish I, Mubareka S, Liles WC (2011) Immunomodulatory therapy for severe influenza. Expert Rev Anti Infect Ther 9: 807-822.
78. Pizzolla A, Smith JM, Brooks AG, Reading PC (2016) Pattern recognition receptor immunomodulation of innate immunity as a strategy to limit the impact of influenza virus. J Leukoc Biol 101: 851-861.
79. Malemud CJ (2009) The discovery of novel experimental therapies for inflammatory arthritis. Mediators Inflamm 2009: 698769.
80. Wortzman ME, Clouthier DL, McPherson AJ, Lin GH, Watts TH (2013) The contextual role of TNFR family members in CD8(+) T-cell control of viral infections. Immunol Rev 255: 125-148.
81. Sarrazin C, Hézode C, Zeuzem S, Pawlotsky JM (2012) Antiviral strategies in hepatitis C virus infection. J Hepatol 56 Suppl 1: 88-100.
82. Helbig KJ, Beard MR (2012) The interferon signaling pathway genes as biomarkers of hepatitis C virus disease progression and response to treatment. Biomark Med 6: 141-150.
83. Pulliam L (2014) Cognitive consequences of a sustained monocyte type 1 IFN response in HIV-1 infection. Curr HIV Res 12: 77-84.
84. Schultz-Cherry S (2015) Role of NK cells in influenza infection. Curr Top Microbiol Immunol 386: 109-120.
85. Magliani W, Conti S, Ciociola T, Giovati L, Zanello PP, et al. Killer peptide: a novel paradigm of antimicrobial, antiviral and immunomodulatory auto-delivering drugs. Future Med Chem 3: 1209-1231.
86. Felix J, Savvides SN (2017) Mechanisms of immunomodulation by mammalian and viral decoy receptors: insights from structures. Nat Rev Immunol 17: 112-129.
87. Shchelkunova GA, Shchelkunov SN (2016) Immunomodulating drugs based on poxviral proteins. BioDrugs 30: 9-16.
88. Rosenthal KS, Mikecz K, Steiner HL, Glant TT, Finnegan A, et al. (2015) Rheumatoid arthritis vaccine therapies: perspectives and lessons from therapeutic ligand epitope antigen presentation system vaccines for models of rheumatoid arthritis. Expert Rev Vaccines 14: 891-908.