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EDITORIAL

Topical biological agents targeting cytokines for the treatment of dry eye disease

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Abstract

Because inflammation plays a key role in the pathogenesis of dry eye disease and Sjögren's syndrome, topical anti-inflammatory agents such as corticosteroids and cyclosporine A have been used to treat inflammation of the ocular surface and lacrimal gland. Systemic biological agents that target specific immune molecules or cells such as tumor necrosis factor (TNF)-α, interferone-α, interleukin (IL)-1, IL-6, or B cells have been used in an attempt to treat Sjögren's syndrome. However, the efficacy of systemic biological agents, other than B-cell targeting agents, has not yet been confirmed in Sjögren's syndrome. Several studies have recently evaluated the efficacy of topical administration of biological agents targeting cytokines in the treatment of dry eye disease. Topical blockade of IL-1 by using IL-1 receptor antagonist could ameliorate clinical signs and inflammation of experimental dry eye. Using a mouse model of desiccating stress-induced dry eye, we have demonstrated that topical application of a TNF-α blocking agent, infliximab, could improve tear production and ocular surface irregularity, decrease inflammatory cytokines and Th-1 CD4+ cells on the ocular surface, and increase goblet cell density in the conjunctiva. Although controversy still remains, the use of topical biological agents targeting inflammatory cytokines may be a promising therapy for human dry eye disease.

Key words: Dry eye disease; Sjögren's syndrome; Biological agent; Tumor necrosis factor-α; Interleukin-1; B cell; Cytokine

Core tip: Although the debate remains about the efficacy of systemic biological agents on Sjögren's syndrome, topical biological agents targeting inflammatory cytokines can be applicable for the treatment of dry eye disease.

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INTRODUCTION

It is well known that tear film hyperosmolarity activates inflammation of the ocular surface, resulting in dry eye disease. Increased expression of inflammatory cytokines, chemokines, matrix metalloproteinases, apoptotic markers, CD4+ Th-1 cells, and Th-17 cells on the ocular surface and in the lacrimal gland have been demonstrated in clinical and experimental dry eye studies[1-15]. Current treatments for dry eye include artificial tears, topical anti-inflammatory agents including corticosteroids and cyclosporine A, punctal plugs, and contact lenses[16-21]. As biological products, variants of serum and plasma, such as autologous serum, umbilical cord serum, and platelet-rich plasma, can also be used topically in severe dry eye[22-25]. Despite these treatments, patients with severe dry eye or

Sjögren's syndrome still complain of discomfort and have signs of persistent inflammation on the ocular surface.

SYSTEMIC BIOLOGICAL AGENTS

Systemic biological agents that target specific immune molecules or cells have been used in an attempt to treat autoimmune diseases such as Sjögren's syndrome. These targets include tumor necrosis factor (TNF)-α, interferone (IFN)-α, interleukin (IL)-1, IL-6, and B cells[26-29].

Although anti-TNF-α agents were found to be successful in modulating other autoimmune diseases, such as rheumatoid arthritis, controversy exists regarding the efficacy of systemic TNF-α blocking agents in Sjögren's syndrome. In a study using a rabbit model of dacryoadenitis, the transfer of a TNF-α inhibitor gene suppressed the appearance of Sjögren's syndrome-like features including reduced tear production and lacrimal gland immunopathology[30]. However, TNF-α inhibitors had no therapeutic effect in an autoimmune murine model of Sjögren's syndrome[31]. In clinical studies, application of a anti-TNF-α agent, infliximab, caused a rapid and sustained improvement in symptoms and signs without any major adverse reaction, whereas it did not show a therapeutic response in patients with primary Sjögren's syndrome compared with controls[32,33]. In addition, oral or subcutaneous administration of etanercept was ineffective in Sjögren's syndrome patients[34,35].

Oral administration of low dose IFN-α showed inconsistent efficacy in various studies but failed to achieve the primary endpoint in a randomized controlled trial[27,36-38]. The efficacy of IL-1 and IL-6 and other cytokines in Sjögren's syndrome is still under investigation[28,29].

In contrast, systemic B-cell targeted therapy has shown clinically promising results in patients with Sjögren's syndrome. Several controlled trials demonstrated considerable improvements in sicca features, salivary flow, ocular surface staining by lissamine green, fatigue, extraglandular manifestations, and quality of life scores after treatment with the B-cell-depleting anti-CD20 antibody, rituximab[39,40]. Although the marked inflammatory infiltrate in the affected glands includes a high percentage of T cell, there is abundant evidence that B cell hyperactivity is a main pathogenic factor in Sjögren's syndrome[41]. Administration of the anti-CD22 antibody, epratuzumab, also showed marked improvements in fatigue and subjective outcomes in patients with Sjögren's syndrome[42]. The B-cell-activating factor (BAFF), which stimulates the production of antibodies by B cells, may be another target for therapy.

TOPICAL BIOLOGICAL AGENTS

Among many targets including cytokines, cytokine signaling pathways, and cell adhesion or leukocyte trafficking, cytokines are the most commonly used therapeutic target for Sjögren's syndrome and inflammatory dry eye. Compared with systemic biological agents for Sjögren's syndrome, only a few studies have evaluated the efficacy of topical administration of biological agents that block pro-inflammatory cytokines in the treatment of dry eyes. Okanobo *et al*[43] demonstrated the therapeutic efficacy of topical blockade of IL-1 in the treatment of experimental dry eye disease. According to their study, application of topical formulations containing 5%IL-1 receptor antagonist (IL-1Ra) was effective in reducing clinical signs and inflammation of dry eye, as evidenced by a decrease in corneal fluorescein staining, the number of central corneal CD11b+ cells, corneal lymphatic growth, and corneal IL-1β expression[43]. The effects by topical IL-1Ra were comparable with those by topical methylprednisolone.

We previously investigated the effects of topical infliximab on the tear film and ocular surface of desiccating stress-induced murine dry eye[44]. Our results showed that mice treated with 0.01% or 0.1% infliximab eye drops had a significant improvement in tear production and corneal surface irregularity. Treated mice also had lower levels of inflammatory cytokines (IL-1β, IL-6, IL-17, IFN-γ, and TNF-α) and Th-1 CD4+ cells and higher goblet cell density in the conjunctiva compared with controls. The reason why the topical anti-TNF-α agent was effective in ocular surface inflammation in contrast to systemic agents could be explained by the dual effect of anti-TNF-α which can enhance T cell receptor-mediated Th1 and Th17 cell activation in peripheral blood and prevent the migration of pathogenic T cells to inflamed tissues, thereby inhibiting inflammation in target tissues[45]. The topical administration of TNF-α blocking agents may be effective in treating dry eye by affecting the inflamed ocular surface directly[44].

Recently, we have reported the therapeutic effect of topical adiponectin, a protein secreted by the adipose tissue, in a mouse model of experimental dry eye[46]. Adiponectin is known to have anti-inflammatory effects as well as anti-diabetic, anti-atherogenic, and anti-angiogenic properties[47-50]. The globular region of adiponectin is structurally similar to TNF-α. Adiponectin can inhibit TNF-α and TNF-α-mediated activation of nuclear factor-κB[51,52]. It can activate adenosine monophosphate-activated protein kinase and protect salivary gland epithelial cells from spontaneous and IFN-γ-induced apoptosis in autoimmune inflammation[53]. CD4+ T-cell-produced IFN-γ plays a pivotal role in Sjögren's syndrome-like conjuntival epithelial apoptosis *via* activation of the extrinsic apoptotic pathway[54]. Our study suggest that topical application of 0.001% or 0.01% globular adiponectin could improve tear production and corneal surface irregularity, decrease levels of inflammatory cytokines (IL-1β, IL-6, TNF-α, IFN-γ, and CXCL9) and Th-1 CD4+ cells in the conjunctiva and lacrimal gland, and could increase conjunctival goblet cell density.

Our experiments show that topical application of a TNF-α blocking agent can improve the tear film and ocular surface parameters by inhibiting inflammatory cytokines, chemokines, and T cells in the conjunctiva and lacrimal glands, and could therefore be useful in the treatment of dry eye disease. Other candidate cytokines

like IL-12, IL-17, and IL-23 may provide promising targets for Sjögren's syndrome. In addition, considering the favorable results of systemic B-cell targeted therapy observed in patients with Sjögren's syndrome, topical B-cell targeting agents such as BAFF could potentially be used as a treatment for autoimmune and inflammatory dry eye.

CONCLUSION

Although some debate still remains about the effect of systemic biological agents on Sjögren's syndrome, topical biological agents that target various inflammatory cytokines can be applicable for the treatment of human dry eye disease. Clinical studies on the safety and efficacy of topical biological agents targeting cytokines in patients with dry eye disease will be needed in the near future.

REFERENCES

1 **Stern ME**, Pflugfelder SC. Inflammation in dry eye. *Ocul Surf* 2004; **2**: 124-130 [PMID: 17216083 DOI: 10.1016/S1542-0124(12)70148-9]
2 **Pflugfelder SC**, Stern ME. Immunoregulation on the ocular surface: 2nd Cullen Symposium. *Ocul Surf* 2009; **7**: 67-77 [PMID: 19383275 DOI: 10.1016/S1542-0124(12)70297-5]
3 **Pflugfelder SC**, de Paiva CS, Li DQ, Stern ME. Epithelial-immune cell interaction in dry eye. *Cornea* 2008; **27** Suppl 1: S9-S11 [PMID: 18813079 DOI: 10.1097/ICO.0b013e31817f4075]
4 **Chen Z**, Tong L, Li Z, Yoon KC, Qi H, Farley W, Li DQ, Pflugfelder SC. Hyperosmolarity-induced cornification of human corneal epithelial cells is regulated by JNK MAPK. *Invest Ophthalmol Vis Sci* 2008; **49**: 539-549 [PMID: 18234997 DOI: 10.1167/iovs.07-0569]
5 **Yoon KC**, Jeong IY, Park YG, Yang SY. Interleukin-6 and tumor necrosis factor-alpha levels in tears of patients with dry eye syndrome. *Cornea* 2007; **26**: 431-437 [PMID: 17457192]
6 **Yoon KC**, De Paiva CS, Qi H, Chen Z, Farley WJ, Li DQ, Pflugfelder SC. Expression of Th-1 chemokines and chemokine receptors on the ocular surface of C57BL/6 mice: effects of desiccating stress. *Invest Ophthalmol Vis Sci* 2007; **48**: 2561-2569 [PMID: 17525185 DOI: 10.1167/iovs.07-0002]
7 **Yoon KC**, Park CS, You IC, Choi HJ, Lee KH, Im SK, Park HY, Pflugfelder SC. Expression of CXCL9, -10, -11, and CXCR3 in the tear film and ocular surface of patients with dry eye syndrome. *Invest Ophthalmol Vis Sci* 2010; **51**: 643-650 [PMID: 19850844 DOI: 10.1167/iovs.09-3425]
8 **Choi W**, Li Z, Oh HJ, Im SK, Lee SH, Park SH, You IC, Yoon KC. Expression of CCR5 and its ligands CCL3, -4, and -5 in the tear film and ocular surface of patients with dry eye disease. *Curr Eye Res* 2012; **37**: 12-17 [PMID: 22029739 DOI: 10.3109/02713683.2011.622852]
9 **Na KS**, Mok JW, Kim JY, Rho CR, Joo CK. Correlations between tear cytokines, chemokines, and soluble receptors and clinical severity of dry eye disease. *Invest Ophthalmol Vis Sci* 2012; **53**: 5443-5450 [PMID: 22789923 DOI: 10.1167/iovs.11-9417]
10 **Moriyama M**, Hayashida JN, Toyoshima T, Ohyama Y, Shinozaki S, Tanaka A, Maehara T, Nakamura S. Cytokine/chemokine profiles contribute to understanding the pathogenesis and diagnosis of primary Sjögren's syndrome. *Clin Exp Immunol* 2012; **169**: 17-26 [PMID: 22670774 DOI: 10.1111/j.1365-2249.2012.04587.x]
11 **Corrales RM**, Stern ME, De Paiva CS, Welch J, Li DQ, Pflugfelder SC. Desiccating stress stimulates expression of matrix metalloproteinases by the corneal epithelium. *Invest Ophthalmol Vis Sci* 2006; **47**: 3293-3302 [PMID: 16877394 DOI: 10.1167/iovs.05-1382]
12 **Yeh S**, Song XJ, Farley W, Li DQ, Stern ME, Pflugfelder SC. Apoptosis of ocular surface cells in experimentally induced dry eye. *Invest Ophthalmol Vis Sci* 2003; **44**: 124-129 [PMID: 12506064 DOI: 10.1167/iovs.02-0581]
13 **Zhang X**, Chen W, De Paiva CS, Corrales RM, Volpe EA, McClellan AJ, Farley WJ, Li DQ, Pflugfelder SC. Interferon-γ exacerbates dry eye-induced apoptosis in conjunctiva through dual apoptotic pathways. *Invest Ophthalmol Vis Sci* 2011; **52**: 6279-6285 [PMID: 21474767 DOI: 10.1167/iovs.10-7081]
14 **Yoon KC**, De Paiva CS, Qi H, Chen Z, Farley WJ, Li DQ, Stern ME, Pflugfelder SC. Desiccating environmental stress exacerbates autoimmune lacrimal keratoconjunctivitis in non-obese diabetic mice. *J Autoimmun* 2008; **30**: 212-221 [PMID: 17988834 DOI: 10.1016/j.jaut.2007.09.003]
15 **Dohlman TH**, Chauhan SK, Kodati S, Hua J, Chen Y, Omoto M, Sadrai Z, Dana R. The CCR6/CCL20 axis mediates Th17 cell migration to the ocular surface in dry eye disease. *Invest Ophthalmol Vis Sci* 2013; **54**: 4081-4091 [PMID: 23702781 DOI: 10.1167/iovs.12-11216]
16 **Alves M**, Fonseca EC, Alves MF, Malki LT, Arruda GV, Reinach PS, Rocha EM. Dry eye disease treatment: a systematic review of published trials and a critical appraisal of therapeutic strategies. *Ocul Surf* 2013; **11**: 181-192 [PMID: 23838019 DOI: 10.1016/j.jtos.2013.02.002]
17 **Dogru M**, Tsubota K. Pharmacotherapy of dry eye. *Expert Opin Pharmacother* 2011; **12**: 325-334 [PMID: 21214414 DOI: 10.1517/14656566.2010.518612]
18 **Doughty MJ**, Glavin S. Efficacy of different dry eye treatments with artificial tears or ocular lubricants: a systematic review. *Ophthalmic Physiol Opt* 2009; **29**: 573-583 [PMID: 19686307 DOI: 10.1111/j.1475-1313.2009.00683.x]
19 **Zhu L**, Zhang C, Chuck RS. Topical steroid and non-steroidal anti-inflammatory drugs inhibit inflammatory cytokine expression on the ocular surface in the botulinum toxin B-induced murine dry eye model. *Mol Vis* 2012; **18**: 1803-1812 [PMID: 22815633]
20 **Utine CA**, Stern M, Akpek EK. Clinical review: topical ophthalmic use of cyclosporin A. *Ocul Immunol Inflamm* 2010; **18**: 352-361 [PMID: 20735287 DOI: 10.3109/09273948.2010.498657]
21 **Roberts CW**, Carniglia PE, Brazzo BG. Comparison of topical cyclosporine, punctal occlusion, and a combination for the treatment of dry eye. *Cornea* 2007; **26**: 805-809 [PMID: 17667613 DOI: 10.1097/ICO.0b013e318074e460]
22 **Kojima T**, Higuchi A, Goto E, Matsumoto Y, Dogru M, Tsubota K. Autologous serum eye drops for the treatment of dry eye diseases. *Cornea* 2008; **27** Suppl 1: S25-S30 [PMID: 18813071 DOI: 10.1097/ICO.0b013e31817f3a0e]
23 **Yoon KC**, Im SK, Park YG, Jung YD, Yang SY, Choi J. Application of umbilical cord serum eyedrops for the treatment of dry eye syndrome. *Cornea* 2006; **25**: 268-272 [PMID: 16633024]
24 **Yoon KC**, Heo H, Im SK, You IC, Kim YH, Park YG. Comparison of autologous serum and umbilical cord serum eye drops for dry eye syndrome. *Am J Ophthalmol* 2007; **144**: 86-92 [PMID: 17493572 DOI: 10.1016/j.ajo.2007.03.016]
25 **Alio JL**, Colecha JR, Pastor S, Rodriguez A, Artola A. Symptomatic dry eye treatment with autologous platelet-rich plasma. *Ophthalmic Res* 2007; **39**: 124-129 [PMID: 17374962 DOI: 10.1159/000100933]
26 **Ng WF**, Bowman SJ. Biological therapies in primary Sjögren's syndrome. *Expert Opin Biol Ther* 2011; **11**: 921-936 [PMID: 21457124 DOI: 10.1517/14712598.]
27 **Tobón GJ**, Saraux A, Pers JO, Youinou P. Emerging biotherapies for Sjögren's syndrome. *Expert Opin Emerg Drugs* 2010; **15**: 269-282 [PMID: 20384543 DOI: 10.1517/14728211003702392]
28 **Roescher N**, Tak PP, Illei GG. Cytokines in Sjogren's syndrome: potential therapeutic targets. *Ann Rheum Dis* 2010; **69**: 945-948 [PMID: 20410069 DOI: 10.1136/ard.2009.115378]

29 **Yamada A**, Arakaki R, Kudo Y, Ishimaru N. Targeting IL-1 in Sjögren's syndrome. *Expert Opin Ther Targets* 2013; **17**: 393-401 [PMID: 23320392 DOI: 10.1517/14728222]

30 **Zhu Z**, Stevenson D, Schechter JE, Mircheff AK, Crow RW, Atkinson R, Ritter T, Bose S, Trousdale MD. Tumor necrosis factor inhibitor gene expression suppresses lacrimal gland immunopathology in a rabbit model of autoimmune dacryoadenitis. *Cornea* 2003; **22**: 343-351 [PMID: 12792478]

31 **Vosters JL**, Yin H, Roescher N, Kok MR, Tak PP, Chiorini JA. Local expression of tumor necrosis factor-receptor 1: immunoglobulin G can induce salivary gland dysfunction in a murine model of Sjögren's syndrome. *Arthritis Res Ther* 2009; **11**: R189 [PMID: 20003451 DOI: 10.1186/ar2888]

32 **Steinfeld SD**, Demols P, Appelboom T. Infliximab in primary Sjögren's syndrome: one-year followup. *Arthritis Rheum* 2002; **46**: 3301-3303 [PMID: 12483735 DOI: 10.1002/art.10674]

33 **Mariette X**, Ravaud P, Steinfeld S, Baron G, Goetz J, Hachulla E, Combe B, Puéchal X, Pennec Y, Sauvezie B, Perdriger A, Hayem G, Janin A, Sibilia J. Inefficacy of infliximab in primary Sjögren's syndrome: results of the randomized, controlled Trial of Remicade in Primary Sjögren's Syndrome (TRIPSS). *Arthritis Rheum* 2004; **50**: 1270-1276 [PMID: 15077311 DOI: 10.1002/art.20146]

34 **Sankar V**, Brennan MT, Kok MR, Leakan RA, Smith JA, Manny J, Baum BJ, Pillemer SR. Etanercept in Sjögren's syndrome: a twelve-week randomized, double-blind, placebo-controlled pilot clinical trial. *Arthritis Rheum* 2004; **50**: 2240-2245 [PMID: 15248223 DOI: 10.1002/art.20299]

35 **Zandbelt MM**, de Wilde P, van Damme P, Hoyng CB, van de Putte L, van den Hoogen F. Etanercept in the treatment of patients with primary Sjögren's syndrome: a pilot study. *J Rheumatol* 2004; **31**: 96-101 [PMID: 14705226]

36 **Cummins JM**, Krakowka GS, Thompson CG. Systemic effects of interferons after oral administration in animals and humans. *Am J Vet Res* 2005; **66**: 164-176 [PMID: 15691053 DOI: 10.2460/ajvr.2005.66.164]

37 **Ship JA**, Fox PC, Michalek JE, Cummins MJ, Richards AB. Treatment of primary Sjögren's syndrome with low-dose natural human interferon-alpha administered by the oral mucosal route: a phase Ⅱ clinical trial. IFN Protocol Study Group. *J Interferon Cytokine Res* 1999; **19**: 943-951 [PMID: 10476942 DOI: 10.1089/107999099313497]

38 **Cummins MJ**, Papas A, Kammer GM, Fox PC. Treatment of primary Sjögren's syndrome with low-dose human interferon alfa administered by the oromucosal route: combined phase Ⅲ results. *Arthritis Rheum* 2003; **49**: 585-593 [PMID: 12910567]

39 **Meijer JM**, Meiners PM, Vissink A, Spijkervet FK, Abdulahad W, Kamminga N, Brouwer E, Kallenberg CG, Bootsma H. Effectiveness of rituximab treatment in primary Sjögren's syndrome: a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2010; **62**: 960-968 [PMID: 20131246 DOI: 10.1002/ar27314]

40 **Dass S**, Bowman SJ, Vital EM, Ikeda K, Pease CT, Hamburger J, Richards A, Rauz S, Emery P. Reduction of fatigue in Sjögren syndrome with rituximab: results of a randomised, double-blind, placebo-controlled pilot study. *Ann Rheum Dis* 2008; **67**: 1541-1544 [PMID: 18276741 DOI: 10.1136/ard.2007.083865]

41 **Tobón GJ**, Pers JO, Youinou P, Saraux A. B cell-targeted therapies in Sjögren's syndrome. *Autoimmun Rev* 2010; **9**: 224-228 [PMID: 19671451 DOI: 10.1016/j.autrev.2009.08.001]

42 **Steinfeld SD**, Tant L, Burmester GR, Teoh NK, Wegener WA, Goldenberg DM, Pradier O. Epratuzumab (humanised anti-CD22 antibody) in primary Sjögren's syndrome: an open-label phase Ⅰ/Ⅱ study. *Arthritis Res Ther* 2006; **8**: R129 [PMID: 16859536]

43 **Okanobo A**, Chauhan SK, Dastjerdi MH, Kodati S, Dana R. Efficacy of topical blockade of interleukin-1 in experimental dry eye disease. *Am J Ophthalmol* 2012; **154**: 63-71 [PMID: 22541929 DOI: 10.1016/j.ajo.2012.01.034]

44 **Li Z**, Choi W, Oh HJ, Yoon KC. Effectiveness of topical infliximab in a mouse model of experimental dry eye. *Cornea* 2012; **31** Suppl 1: S25-S31 [PMID: 23038030 DOI: 10.1097/ICO.0b013e31826a80ea]

45 **Bosè F**, Raeli L, Garutti C, Frigerio E, Cozzi A, Crimi M, Caprioli F, Scavelli R, Altomare G, Geginat J, Abrignani S, Reali E. Dual role of anti-TNF therapy: enhancement of TCR-mediated T cell activation in peripheral blood and inhibition of inflammation in target tissues. *Clin Immunol* 2011; **139**: 164-176 [PMID: 21334981 DOI: 10.1016/J.clim.2011.01.015]

46 **Li Z**, Woo JM, Chung SW, Kwon MY, Choi JS, Oh HJ, Yoon KC. Therapeutic effect of topical adiponectin in a mouse model of desiccating stress-induced dry eye. *Invest Ophthalmol Vis Sci* 2013; **54**: 155-162 [PMID: 23211823 DOI: 10.1167/iovs.12-10648]

47 **Wolf AM**, Wolf D, Rumpold H, Enrich B, Tilg H. Adiponectin induces the anti-inflammatory cytokines IL-10 and IL-1RA in human leukocytes. *Biochem Biophys Res Commun* 2004; **323**: 630-635 [PMID: 15369797]

48 **Wulster-Radcliffe MC**, Ajuwon KM, Wang J, Christian JA, Spurlock ME. Adiponectin differentially regulates cytokines in porcine macrophages. *Biochem Biophys Res Commun* 2004; **316**: 924-929 [PMID: 15033490]

49 **Neumeier M**, Weigert J, Schäffler A, Wehrwein G, Müller-Ladner U, Schölmerich J, Wrede C, Buechler C. Different effects of adiponectin isoforms in human monocytic cells. *J Leukoc Biol* 2006; **79**: 803-808 [PMID: 16434692]

50 **Okamoto Y**, Folco EJ, Minami M, Wara AK, Feinberg MW, Sukhova GK, Colvin RA, Kihara S, Funahashi T, Luster AD, Libby P. Adiponectin inhibits the production of CXC receptor 3 chemokine ligands in macrophages and reduces T-lymphocyte recruitment in atherogenesis. *Circ Res* 2008; **102**: 218-225 [PMID: 17991878]

51 **Maeda N**, Shimomura I, Kishida K, Nishizawa H, Matsuda M, Nagaretani H, Furuyama N, Kondo H, Takahashi M, Arita Y, Komuro R, Ouchi N, Kihara S, Tochino Y, Okutomi K, Horie M, Takeda S, Aoyama T, Funahashi T, Matsuzawa Y. Diet-induced insulin resistance in mice lacking adiponectin/ACRP30. *Nat Med* 2002; **8**: 731-737 [PMID: 12068289]

52 **Tilg H**, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. *Nat Rev Immunol* 2006; **6**: 772-783 [PMID: 16998510]

53 **Katsiougiannis S**, Tenta R, Skopouli FN. Activation of AMP-activated protein kinase by adiponectin rescues salivary gland epithelial cells from spontaneous and interferon-gamma-induced apoptosis. *Arthritis Rheum* 2010; **62**: 414-419 [PMID: 20112400 DOI: 10.1002/art.27239]

54 **Zhang X**, Chen W, De Paiva CS, Volpe EA, Gandhi NB, Farley WJ, Li DQ, Niederkorn JY, Stern ME, Pflugfelder SC. Desiccating stress induces CD4+ T-cell-mediated Sjögren's syndrome-like corneal epithelial apoptosis via activation of the extrinsic apoptotic pathway by interferon-γ. *Am J Pathol* 2011; **179**: 1807-1814 [PMID: 21843497 DOI: 10.1016/j.ajpath.2011.06.030]

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

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Standard abbreviations should be defined in the abstract and on first mention in the text. In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Permissible abbreviations are listed in Units, Symbols and Abbreviations: A Guide for Biological and Medical Editors and Authors (Ed. Baron DN, 1988) published by The Royal Society of Medicine, London. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, mAb, can be used directly without further explanation.

Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
Genotypes: *gyrA*, *arg* 1, *c myc*, *c fos*, *etc.*
Restriction enzymes: *Eco*RI, *Hin*dI, *Bam*HI, *Kbo* I, *Kpn* I, *etc.*
Biology: *H. pylori*, *E coli*, *etc.*

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