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Review

Suppression of Mast Cell Activation by Glucocorticoid

HIDESHI YOSHIKAWA and KACHIO TASAKA*

Department of Parasitology and Immunology, Yamanashi Medical University, 1110 Shimokato, Tamaho-cho, Yamanashi 409-3898, Japan

Abstract. Mast cells play a critical role in allergic diseases. When mast cells are activated by cross-linking of their high affinity IgE receptors by the antigen and IgE antibodies, release of chemical mediators is followed by secretion of multiple cytokines. We report that IL-3-dependent mucosal-type mast cells undergo apoptosis when IL-3 is withdrawn. In addition, cross-linking of high affinity IgE receptors prevents apoptosis of mast cells by paracrine mechanisms, producing IL-3, IL-4 and granulocyte/macrophage colony-stimulating factor (GM-CSF). However, the secretion of endogenous growth factors are not enough for cell survival, whereas IL-4 induces cell aggregation by expressing adhesion molecules such as leukocyte function-associated antigen 1 (LFA-1), and makes it reactive to endogenous growth factors by contact cell to cell interaction. On the other hand, dexamethazone down-regulates the expression of intracelluar adhesion molecule 1 (ICAM-1) and IL-4 in activated mast cells, by which the self-aggregation of mast cells is inhibited and apoptosis is induced. Thus, glucocorticoids suppress mast cell survival by inhibiting IL-4 production and expression of adhesion molecules.

Key words: allergy; mast cell; glucocorticoid; cytokine; adhesion molecule.

Introduction

Glucocorticoid (GC) is primarily used for the treatment of autoimmune diseases and some allergic diseases and its clinical effectiveness has been well recognized. GC is administered systemically to patients with allergic diseases such as anaphylactic shock or severe bronchial asthma, and steroid ointment is used to treat dermatological diseases such as atopic dermatitis. In addition, steroid inhalation therapy has become the main mode of therapy for bronchial asthma in recent years. Hence, it has become clear that GC can suppress the onset and prolongation of allergic diseases. Unlike other drugs, GC suppresses the immune system by affecting many of its facets and various immunocompetent cells, and it is believed that messenger RNAs (or proteins) that are suppressed by GC vary from one cell type after another. It is generally accepted that GC is clinically effective in treating different immunological diseases since it affects a wide variety of immunosuppression mechanisms. Mast cells are important in allergic disease since they function as effector cells, indicating that mast cells may be the target of GC in the suppression of allergic disease. Therefore, we summarize here the relationship between mast cells and type-I allergy and discuss the effects of GC on mast cells and its immunosuppressive mechanisms.

Mast Cells and Cytokines

In the development of allergic diseases, allergen--specific IgE antibodies are produced and mast cells are

* Correspondence to: Kachio Tasaka, M. D. Ph. D., Department of Parasitology and Immunology, Yamanashi Medical University, 1110 Shimokato, Tamaho-cho, Yamanashi 409-3898, Japan, tel.: +81 55 273 11 11 (ext. 2281), fax: +81 55 273 95 42, e-mail: ktasaka@res.yamanashi-med.ac.jp

activated when high affinity IgE receptors (FcεRI) are cross-linked by the antigen and IgE antibodies. Next, these activated mast cells release chemical mediators to induce the immediate-phase of allergic responses. At the same time, these activated mast cells regulate the gene expression of various inflammatory and Th2-type cytokines. Consequently, eosinophils infiltrate into inflammatory sites and inflammatory cells induce delayed-phase allergic responses (Fig. 1). It is thought that different subtypes of mast cells produce different cytokines, in other words, IL-3-dependent mucosal-type mast cells derived from murine bone marrow express IL-4 and IL-13, whereas stem cell factor (SCF)-dependent connective tissue-type mast cells express IL-12[23]. The cytokines produced by murine mast cells act as the growth factors of these mast cells. IL-3 not only induces the proliferation of IL-3-dependent mucosal-type mast cells, but also prevents apoptosis caused by a lack of IL-3 (Fig. 2). This is enhanced by the presence of IL-4 or IL-10, and is maximized when all three of these cytokines are present[25]. However, neither IL-4 nor IL-10 alone functions as a growth factor. Furthermore, it has been reported that IL-3 and IL-4 act synergistically with SCF to promote the proliferation of SCF-dependent connective tissue-type mast cells. Studies on human mast cells are behind those on rodent mast cells. To date, SCF is the only known growth factor of human mast cells. In humans, the expression of c-kit, a ligand of SCF, is suppressed by IL-4, which results in the suppressed proliferation of mast cells. Hence, IL-4 appears to have slightly different functions in mice and humans[27]. On the other hand, the cytokines produced by mast cells also induce the expression of adhesion molecules and are involved in the progression of inflammation. IL-4 and TNF-α enhance the expression of adhesion molecules such as intracelluar adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1) and endothelial leukocyte adhesion molecule 1 (ELAM-1) on vascular endothelial cells and activate the infiltration of lymphocytes, mast cells and eosinophils into inflammtory sites[28].

In general, cytokines are produced by not only mast cells, but also by T cells and other types of cells. Th cells have two subsets: Th1 cells, which produce IL-2 and IFN-γ, and Th2 cells, which produce IL-4, IL-5, IL-6, IL-10 and IL-13. Generally, in allergic disease, the Th1/Th2 balance is skewed to Th2 dominance, resulting in an immune response mediated by humoral immunity, but the initial differentiation of Th2 is IL-4-

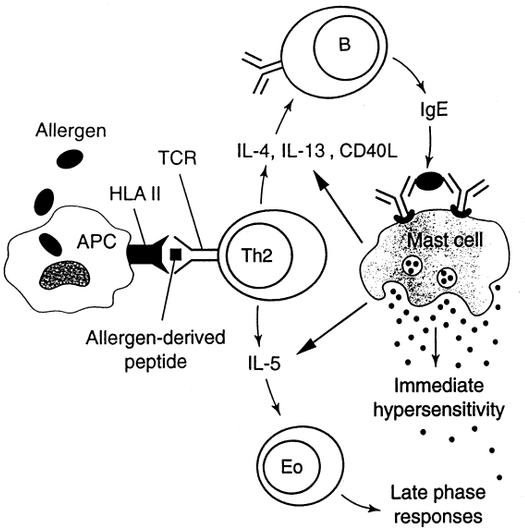


Fig. 1. The role of mast cells in the allergic immune response. Upon entry into the human body, the allergen is taken up and processed by an APC. The presented allergen-derived peptide is recognized by an allergen-specific Th2-like cells that produce IL-4, IL-13 and express CD40L. IL-4, IL-13 and CD40L induce the isotype switch to IgE in B cells. IgE binds to the high affinity Fcε-receptor on mast cells, which degranulate upon Fcε-receptor cross-linking, resulting in the immediate-phase of allergic response. Activated mast cells also produce IL-4, IL-13 and express CD40L, and enhance allergic immune response. IL-5 produced by the Th2-like and mast cells plays a role in the differentiation and survival of eosinophils, which are responsible for the late-phase response, especially in allergic asthma. APC – antigen presenting cell, Eo – eosinophils, HLA II – human leukocyte antigen class II, TCR – T cell receptor, Th2 – T helper 2 cell

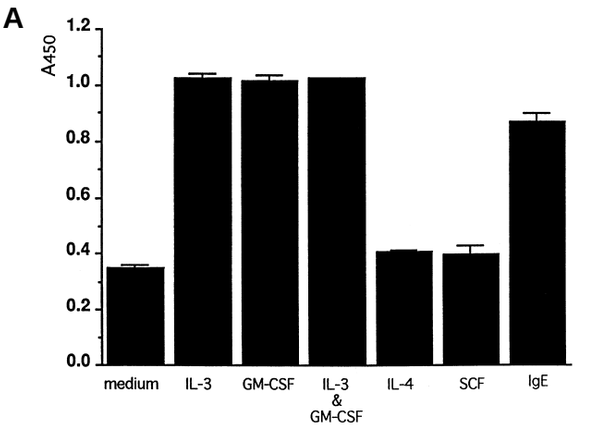
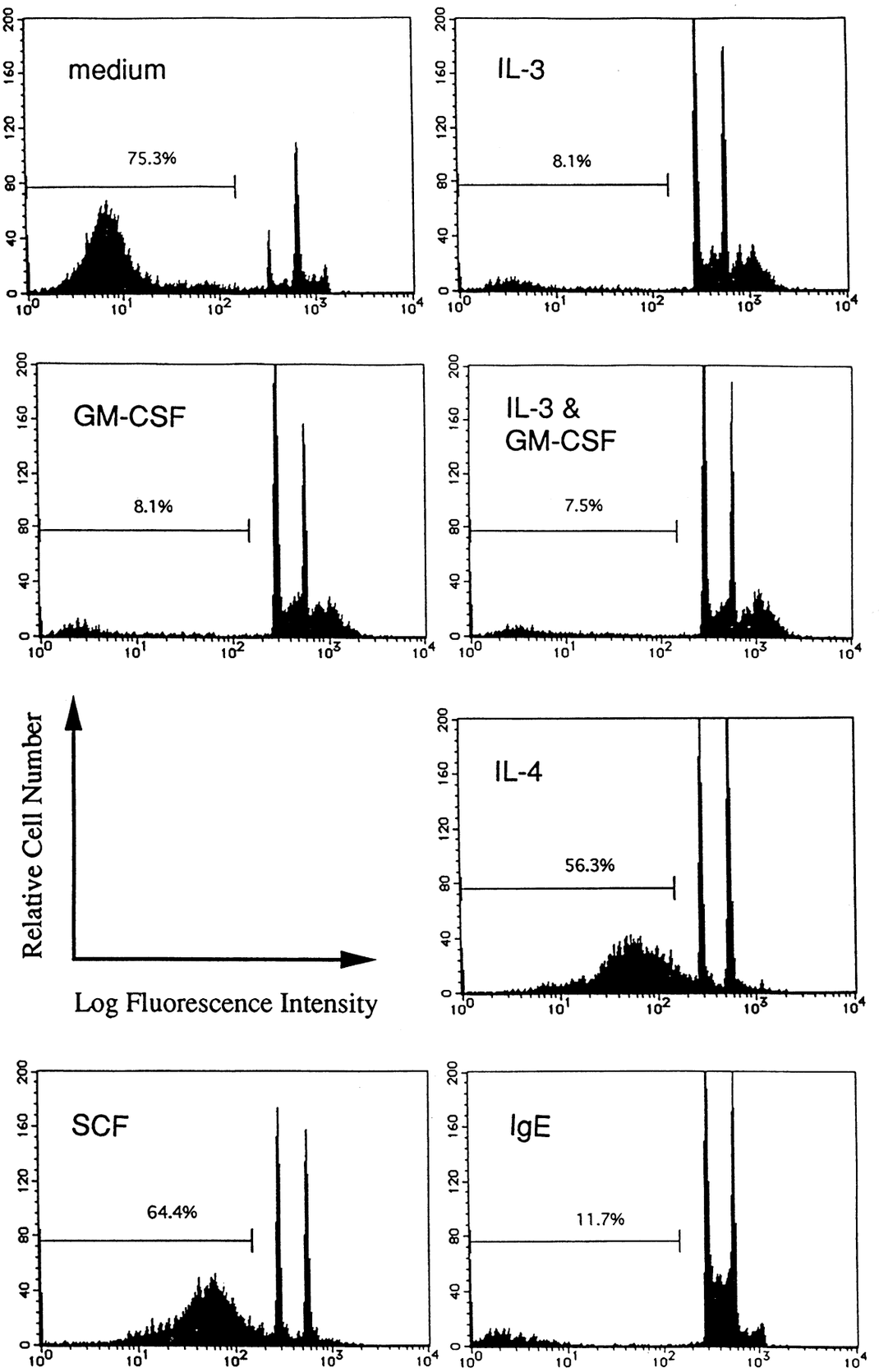


Fig. 2. The viability of mouse mast cells (MC9) stimulated with exogenous cytokines or cross-linking of high affinity Fcε-receptor. **A** – the MC9 cells were cultured with medium alone, rIL-3 (50 U/ml), rGM-CSF (50 U/ml), or a combination of rIL-3 and rGM--CSF, rIL-4 (50 U/ml), or rSCF (50 U/ml). The MC9 cells were also cultured with anti-DNP IgE (10 μg/ml) and DNP-albumin (500 ng/ml). After 48 h culture, the viability was examined by a Cell Counting Kit-8. **B** – the MC9 cells were cultured with the same dose of cytokines or anti-DNP IgE and DNP-albumin. After 48 h, cells were stained with propidium iodide. Percentages of apoptotic cells were determined using flow cytometer[32]

B


medium
75.3%
IL-3
8.1%
GM-CSF
8.1%
IL-3 &
GM-CSF
7.5%
Relative Cell Number
Log Fluorescence Intensity
IL-4
56.3%
SCF
64.4%
IgE
11.7%

-dependent. Therefore, IL-4-producing mast cells, basophils and NKT cells may be deeply involved in the initial differentiation of Th2 cells. On the other hand, IL-12 is a cytokine produced by macrophages, and it accelerates the differentiation of Th1 cells. Since this reaction is suppressed by IL-4, the Th1/Th2 balance can be mutually influenced[18]. Furthermore, IL-4 and IL-13 independently activate IgE induction in B cells and accelerate the transcription of the Cε gene. The expression of this gene plays an important role in the subsequent IgE class switch[21]. Therefore, cytokines originating from mast cells, including IL-4, may be involved in the onset or progression of allergic diseases.

Allergic Diseases and Cytokines

IL-4 is one of the cytokines that are often studied due to their association with allergic diseases. In fact, elevated IL-4 production has been confirmed in patients with bronchial asthma or atopic dermatitis. Also, it has been documented that IL-4 production is suppressed in patients with allergic diseases who are undergoing desensitization therapy[20]. The results of an animal study using IL-4 gene transgenic mice showed elevated IL-4 production and higher levels of serum IgE, and such induced symptoms as conjunctivitis were observed[24]. As is the case with bronchial asthma, allergic rhinitis, dermatitis and conjunctivitis in humans, cellular infiltration consisting of mast cells and eosinophils is observed, thus showing that these transgenic mice could serve as animal models of human allergic disease. On the other hand, in IL-4 gene knock-out mice, IgE production and allergic reactions are markedly reduced[11, 26]. Furthermore, recently established inbred NC/Nga mice are receiving a lot of research attention due to the fact that they spontaneously develop dermatitis which is very similar to atopic dermatitis. In these mice, increased serum IgE and strong IL-4 positive reactions in their activated mast cells and Th cells are observed[13]. As for as the relationship between elevated IL-4 production and mast cells in allergic disease, Th2 cells, NK T cell, basophils and mast cells produce IL-4, but since IL-4 is essential for the initial differentiation of Th2 cells, mast cells must be the important source of IL-4 in the induction of allergic reactions. In fact, data supporting this view have been obtained by different human and mouse studies[1, 3, 17]. Furthermore, it has been shown that IL-4 and IL-5 are synthesized and secreted by bronchial mucosal mast cells in bronchial asthma or by nasal mucosal mast cells in allergic rhinitis[31].

IgE antibody production (class switch) is one of the facets of allergic disease affected by IL-4. In addition, this particular cytokine enhances the expression of VCAM-1, an adhesion molecule of vascular endothelial cells, to induce the tissue infiltration of eosinophils expressing VLA-4. The results of animal studies using asthmatic guinea pigs showed that eosinophil infiltration was inhibited by the administration of anti-VLA-4 antibodies[10]. In addition, as in the present study, it has been reported that IL-4 induces the expression of LFA-1 and ICAM-1 on mast cells, suggesting that these factors may be deeply involved in delayed-phase allergic responses such as infiltration of inflammatory cells[31]. Furthermore, it is becoming clear that bronchial asthma and atopic dermatitis are actually chronic eosinophilic infiltration. IL-5 is a selective differentiation and activation factor of eosinophils and is essential for the infiltration of eosinophils into inflammtory sites. Many studies have found elevated IL-5 production in inflammatory sites accompanied by an infiltration of eosinophils[4]. In addition, the level of IL-5 production has been reported to be significantly higher in patients with bronchial asthma than in healthy individuals. It is thus clear that IL-4 and IL-5 are closely involved in the pathogenesis of allergic disease.

Immunosuppressive Action of GC

GC suppresses the immune system by affecting not only immunocompetent cells including lymphocytes, monocytes, granulocytes, vascular endothelial cells and fibroblasts, but also other types of cells. This is also supported by the finding that side-effects of GC vary greatly (hypertension, diabetes, gastric ulcer, cataract and mental disorder). Furthermore, GC regulates different messenger RNAs and proteins in different cells. It is generally accepted that GC suppresses the immune system by strongly affecting lymphocytes, in particular T cells, but not B cells. In fact, moderate amounts of GC administration do not reduce the level of immunoglobulins. The effects of GC on T cells can be divided into two parts: the reduction of the number of T cells and the suppression of cytokine production in T cells. The former is caused by apoptosis of immature and activated T cells and the latter by marked reductions in IL-2 production, thus suppressing the immune system[2, 14, 16]. In addition, GC suppresses various cytokines secreted from activated T cells (IL-3, -4, -5, -6, IFN-γ and TNF-α) and cytokines secreted from cells other than T cells[30].

Additionally, GC is known to inhibit inflammation by suppressing the expression of adhesion molecules

which are being closely examined as immunological and inflammatory mediators. It has been suggested that GC suppresses the expression and function of adhesion molecules such as ICAM-1 and ELAM-1, expressed on vascular endothelial cells, which are essential for the induction of inflammatory cell infiltration[5].

Suppressive Effect of GC on Mast Cell Activation

Even though GC suppresses the immune system in a variety of ways, its action is mediated by the GC receptor (GR). It is thought that this receptor can be found in most cells in the body, including mast cells. After GC binds to GR, the resulting complex migrates into the nucleus and binds to a section of DNA that has a specific sequence near a target gene to regulate its transcription by affecting various nucleoproteins and other transcription factors. As mentioned above, in the delayed-phase of allergic response, the cytokines produced by mast cells, in particular IL-4, IL-5 and adhesion molecules, are believed to play an important role. We found that cross-linking of the FcεRI of mast cells induces or enhances the production of various cytokines, including IL-4 and IL-5, and that IL-4 enhances intercellular adhesion by regulating the expression of adhesion molecules (Fig. 3, 4). It is generally accepted that the action of GC in allergic disease is more pronounced during its delayed-phase than during the immediate-phase, and the reason for this may be largely attributable to GC's ability to suppress cytokine production by regulating their gene expression. GC affects mast cells and T cells slightly differently, since it does not induce apoptosis in mast cells alone. However, in order to effectively function in inflammatory sites, the concentrations of these growth factors, which are required for the survival of mucosal-type mast cells, must remain relatively high by intercellular adhesion. IL-4 production, induced by mast cell activation, leads to the expression of adhesion molecules and the induction of intercellular adhesion, and the survival of mast cells is maintained by the supply of growth factors attributable to intercellular paracrine. The production of IL-4 in mast cells and the suppression of ICAM-1 caused by GC eventually bring about a regional deficiency of growth factors, causing apoptosis of mast cells[32]. The same phenomenon is also seen in terms of the SCF/c-kit interaction between fibroblasts and connective tissue--type mast cells. GC indirectly reduces the number of mast cells by suppressing the SCF expression of fibroblasts and blocking the suppressing the SCF expression

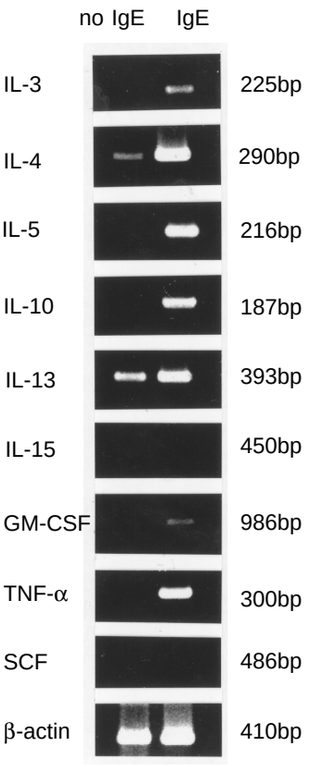


Fig. 3. RT-PCR analysis of mRNA expression for cytokines induced by MC9 cells via cross-linking of high affinity Fcε-receptor. MC9 cells were cultured with medium alone (no IgE) or anti-DNP IgE and DNP-albumin (IgE) for 4 h. Total RNA from cultured MC9 cells were reverse transcribed and PCR amplified. Products using primers for each cytokine were resolved in agarose gels and visualized by staining with ethidium bromide[32]

of fibroblasts and blocking the necessary signals for the survival of connective tissue-type mast cells[6].

Finally, in terms of the suppressive mechanism of GC on gene expression, activated GR is known to interact with AP-1, NF-κB, redox signal and other nuclear receptors (Fig. 5)[8, 12, 15, 29]. We believe that the suppression of ICAM-1 expression in mast cells by GC was mediated by an interaction between GR and NF--κB. Furthermore, with regards to the GC-induced suppression of IL-4 production in activated mast cells, it has been reported that the binding site of transcription factors such as NF-AT family and c-Maf that are involved in IL-4 transcription are present in the promotor region of the murine IL-4 gene, and that GATA-3 binds to the IL-4 promotor and activates transcription; thus, this series of reaction may interact with GR[9, 19]. However, a recent study reported that the IL-4 production by mast cells does not require c-Maf[22]. An enhancer region including PU. 1 and GATA was recently found in the intron of the IL-4 gene of mast cells, suggesting

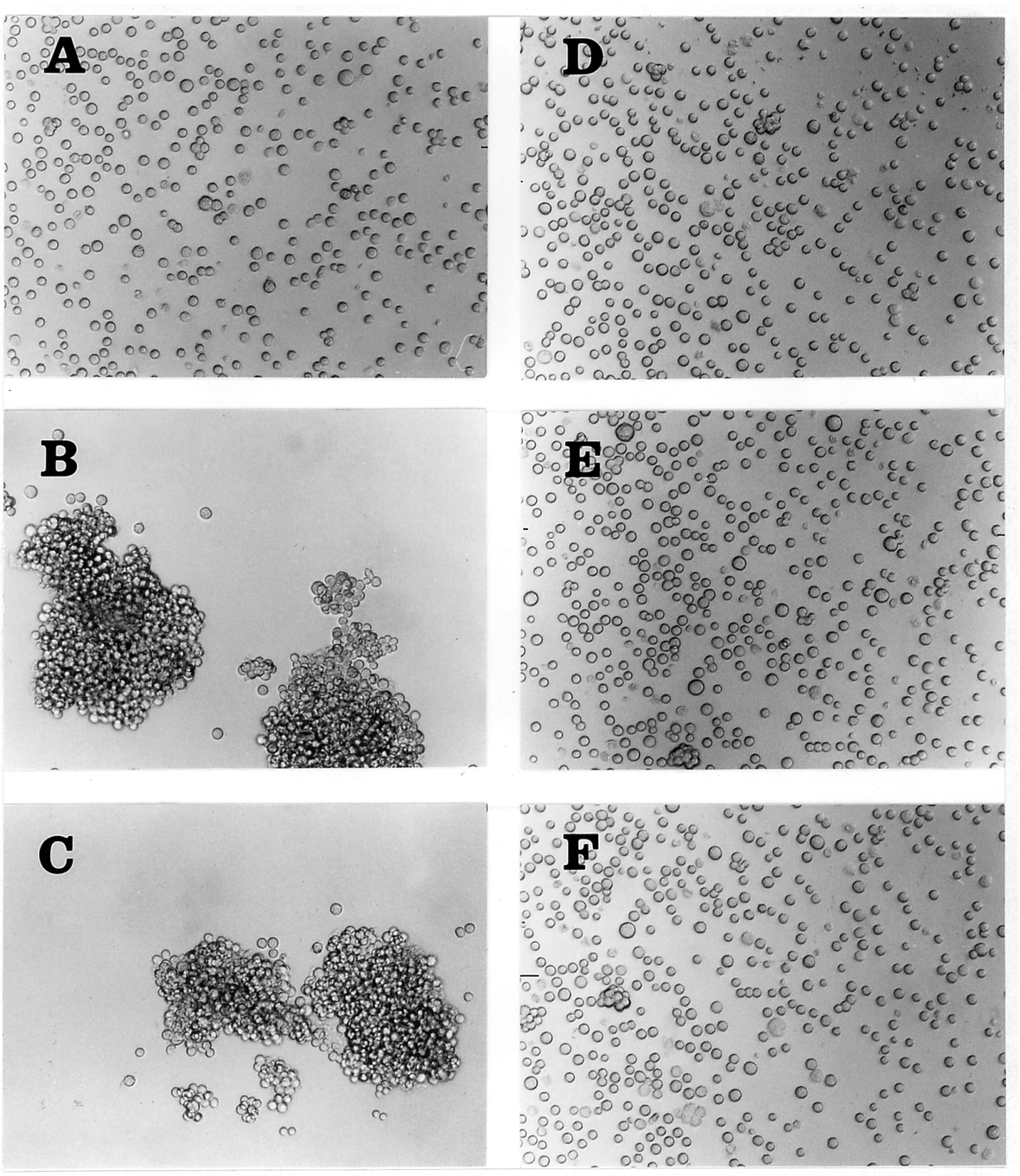


Fig. 4. Self-aggregation of MC9 cells cultured with cytokines or cross-linking of high affinity Fcε-receptor. A total of 1×10^6/10 ml MC9 cells was cultured in dishes with **A** – rIL-3 (50 U/ml), **B** – rIL-3 (50 U/ml) and rIL-4 (50 U/ml), and **C** – anti-DNP IgE and DNP-albumin. **D**, **E**, **F** – a total of 50 μg/ml of anti-LFA-1α monoclonal antibody was added to each culture of **A**–**C**. The cells were incubated for 12 h and photographed

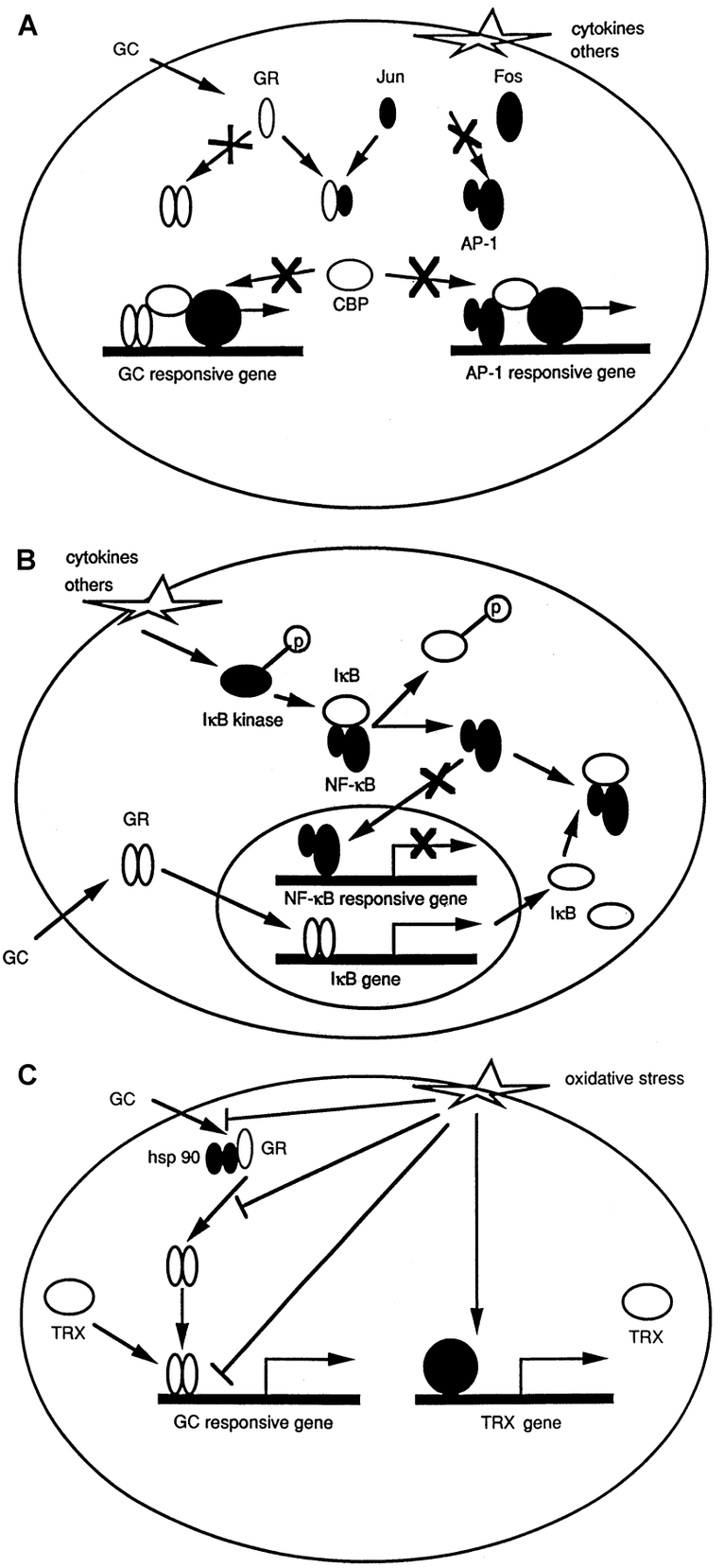


Fig. 5. The mechanisms of inhibition of transcriptional activities by GC. **A** – the activated GR forms heterodimer with Jun and inhibits the formation of AP-1 as the heterodimer of Jun and Fos. GR also inhibits the activity of AP-1 by binding to CBP, an adapter protein, which is required for the transcriptional activity of AP-1. **B** – the activated GR induces expression and production of excess amount of IκB, which bind to the activated NF-κB, resulting in the inhibition of transcriptional activity of NF-κB. **C** – under oxidative stress, binding of GC to GR, GC-dependent release of hsp 90 from GR and transportation of GR to the nucleus are inhibited, resulting in the inhibition of expression of GC-response genes. CBP – cyclic AMP binding protein, GC – glucocorticoid, GR – glucocorticoid receptor, hsp 90 – heat shock protein 90, TRX – thioredoxin

the existence of a regulatory mechanism of the IL-4 gene that is specific to mast cells[7].

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