IgG Receptors and Interferons in Skin and Serum from Healthy Individuals and Patients with Psoriasis

Maya Tigalonova
Oslo Hudklinikk, Hegdehaugsv. 36B, N-0352 Oslo, Norway

This work was conducted at the Department of Dermatology, Ullevaal Hospital, University of Oslo, the Broegelmann Research Laboratory for Microbiology and the Department of Dermatology, University of Bergen, Norway.

Dr Maya Tigalonova (*middle*) defended her Thesis on January 29th, 2000, at the University of Oslo. Faculty opponents were (*from left*) Professor Christian Vedeler, Department of Neurology, Haukeland University Hospital, Bergen, Professor Edvard S. Falk, Department of Dermatology, University of Tromsø, and Professor Ole Fyrand, Department of Dermatology, The National Hospital, University of Oslo. Chairman was Professor Erik Qvigstad (*right*), University of Oslo.

The first part concerns studies on receptors for the Fc-part of IgG (FcR) on epidermal cells in normal human skin, and the second part studies on FcR and other inflammatory parameters in patients with psoriasis before and during different treatments.

FcR comprise a heterogenous group of molecules which act as key molecules in the immune system by allowing and mediating immune interactions between various cells and IgG of different classes and subclasses. FcR are expressed on various cells which normally participate in immune reactions, such as monocytes, macrophages, granulocytes and lymphocytes, but have also been demonstrated on cells which normally do not belong to the immune system, such as trophoblasts and epithelial cells in the placenta, and on intestinal epithelium. Cells infected with virus acquire or enhance the expression of FcR. Finally, FcR have been demonstrated in soluble form in normal sera and in sera from patients with various diseases. FcR can be demonstrated on cells in suspension and in tissue sections using functional assays and assays with polyclonal or monoclonal MoAbs. Three distinct classes of human leucocyte FcR have been characterized. FcR I is a high-affinity receptor. FcR II and FcR III are low-affinity receptors. All three classes of FcR belong to the IgG supergene family and are integral membrane proteins with an amiono-terminal extracellular portion and a carboxy-terminal cytoplasmic "tail". The extracellular domains mediate binding of the ligands, whereas the cytoplasmic tail mediates intracellular signals.

Langerhans' cells (LC) in suspension express FcR, but the receptors had not previously been detected in skin sections. Using the binding of soluble immune complexes (IC) to cryostat sections of normal skin in an indirect immunofluorescence assay it was clearly shown that LC express FcR *in situ*. Complexed IgG had a much higher capacity to block the FcR activity than native IgG indicating that LC have low affinity FcR. In addition, a monoclonal antibody (MoAb) against the low affinity FcR II (CDw32, IV.3) reacted with most LC. When freshly prepared EC from normal skin were examined, >95% of LC bound the soluble IC, while >90% of the CD1a+ cells were stained with IV.3, which were the only anti-FcR MoAb reacting with LC.

Keratinocytes (KC) expressed FcR activity which was different from that on LC. The MoAb 32.2 against FcR I gave weak granular staining along the outer aspect of KC not only in stratum spinosum, but also in stratum granulosum where the receptor activity was strongest.

The wide distribution of FcR in normal epidermis, with strongest activity in the subcorneal layer, points to an active physiological role of IgG and its receptors in the skin immune system. The receptors may be involved in several functions under physiological as well as pathological conditions. The receptors might be:

- protective with the capacity to bind IC and IgG against harmful antigens.
- involved in IgG transport through epidermis.
- of immunoregulatory importance via cytokines released as result of IgG or IC binding.

FcR in cryostat sections of lesional skin from 8 patients with stationary plaque psoriasis and 12 patients with highly active psoriasis were examined for FcR activity. The FcR-like molecule annexin II (AA) in serum were measured in an enzyme linked immunoabsorbent assay (ELISA) with the MoAb B1D6. The patients were treated with cyclosporine (n=5), acitretin (n = 7) and Goeckerman regimen (n = 8). As controls served 8 skin biopsies and 22 sera from healthy individuals. Highly active psoriatic lesions showed strongest activity for FcR I, II and III, as well as IC binding. The FcR+ mononuclear cells were located perivascularly and along the dermo-epidermal junction. The large proportion of FcR+ histiocytes in the clinically most active lesions sustains the concept of a local immune reaction early in the disease process. The FcR activity detected *in situ* decreased paralleling the improvement following therapy. Epidermal LC in psoriatic skin lesions were positive for FcR II and immune complex binding. The strongest IC binding to LC was noted in highly active psoriatic lesions. The FcR activity on LC decreased during therapy. AA levels were lower in sera from patients with psoriasis than in controls, and not correlated to disease activity. In 4 patients the FcR levels increased during therapy. The reduced levels of FcR in psoriatic sera might be due to consumption in the skin or to anti-FcR autoantibodies.

Skin sections of lesional skin from 5 patients with severe psoriasis were examined before and during cyclosporine treatment. During therapy the dermal accumulation of T-lymphocytes (CD3+, CD4+, CD8+ and IL2R+ cells), macrophages (OKM1+), CD1a+ and FcR+ cells decreased, paralleling clinical improvement. However, in normalized skin there were still patchy accumulations of mononuclear cells in some dermal papillae close to the dermo-epidermal junction. In the epidermis CD8+ and IL2R+ cells rapidly disappeared during clinical improvement. The numbers of epidermal dendritic CD1a+ and HLA-DR+ cells increased and their distribution pattern became regular. The percentage of CD1a+ epidermal cells expressing FcR was reduced during therapy.

Sera from 52 patients with psoriasis and 106 controls were tested for IFN-γ, IFN-α2 and TNF-α in ELISA and for total IFN activity using an infectivity inhibition micromethod. Psoriasis patients had lower serum levels of IFN-γ than the controls. The highest median serum INF-γ levels were in patients with peripherally spreading psoriasis. Patients with stable plaque psoriasis showed lower serum IFN-γ levels as compared with other forms of psoriasis or with blood donors.

The serum levels of IFN-α2, total IFN activity and TNF-α did not differ between the psoriasis and control group. Treatment with cyclosporine, acitretin and the Goeckerman regimen increased the total IFN activity.

List of original publications

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4. Bjerke JR, Tigalonova M, Matre R. Fcγ-receptors in stratum granulosum: An immune defense in normal human skin? Acta Derm Venereol 1994; 74: 429–432.
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7. Tigalonova M, Bjerke JR, Gallati H, Degré M, Majewski S, Jablonska S, Matre R. Serum levels of interferons and TNF-α are not correlated to psoriasis activity and therapy. Acta Derm Venereol 1994; Suppl. 186: 25–27.