L35. Fc receptors and cell activation

Receptors to the Fc region (Fc receptors, FcR) of immunoglobulins (Ig) are expressed by many cell types, particularly phagocytes. There are five main types of FcR depending on their ligand specificity; FcεR which bind IgE, FcγR which bind IgG and finally FcγRI that bind IgM [1]. Cross-linking of FcR by immune complexes usually initiates immunoreceptor-tyrosine activation motif (ITAM)-dependent cellular responses through ITAM-containing FcγRIy subunit. The FcγRIγ-chain ITAM consists of a conserved stretch of paired tyrosines and leucines separated by seven amino acids in a consensus sequence (YxxLx_2YxxL). The Src kinase Lyn phosphorylates the tyrosines within the associated FcγRIy ITAM. These then serve as “docking” sites for the recruitment of the tyrosine kinase Syk which facilitates the activation of multiple targets such as PI3K and induces the downstream release of IP3 and diacylglycerol to trigger calcium release. Moreover, Src family kinases, which are activated after FcR stimulation, also induce the formation of multimolecular adaptor protein complexes responsible for the activation of Raf-1 – MEK – MAP kinases by sequential phosphorylation. The interconnected signaling pathways couple FcγRIγ-chain ITAM phosphorylation to different cellular processes, such as gene expression by the activation of several transcription factors (including nuclear factor-κB and AP-1). The ligation of FcRs by immune complexes can trigger numerous activating cellular effector functions including phagocytosis, antibody-dependent cellular cytotoxicity and the secretion of cytokines or other inflammatory mediators [2]. Thus, FcRs provide a crucial link between the humoral and the cellular arms of the immune system.

FcRs are expressed either as membrane bound receptors or as soluble receptors. Most membrane FcRs consist of an extracellular immunoglobulin binding domain, a transmembrane domain and an intracellular domain that may contain signaling functions. However, for the majority of FcRs the signaling domain is contained in the associated signaling adaptors such as FcγRIy and in some cases the FcγRI. The properties of the intracellular domain determine the outcome of FcR-mediated signaling. Activating FcRs bear ITAM whereas inhibitory FcRs bear either an intracellular immunoreceptor-tyrosine-based inhibitory motif (ITIM) or inhibitory ITAM [3]. These antagonistic signals play a key role in the control of cell responses. This balance is of great importance to prevent tissue damage through an exaggerated activation of the immune system and to maintain homeostasis. Negative signaling in the immune system classically involves phosphatases which prevent or abort kinase-dependent activating signaling. Inhibitory receptors containing ITIMs in their cytoplasmic domain co-aggregate with ITAM-containing activating receptors. Kinases associated with ITAMs induce the tyrosine phosphorylation of juxtaposed ITIMs. This results in the recruitment of phosphatases to the phosphorylated ITIMs, which are exquisitely localized to abrogate the ITAM-dependent positive signal. It has been recently demonstrated that ITAMs can also propagate inhibitory signals when they are in a conformation that we have named inhibitory ITAM (ITAMI). Some FcRs, such as FcαRI and FcγRIIA, when associated with the ITAM-bearing adaptor FcγRIy, can act as bi-functional receptors which may trigger inhibitory signals toward a whole array of activating receptors and down-regulate IgE- or IgG-, Fc-receptor-mediated, signaling. The ITAMI function is initiated by targeting these FcRs at a low valency and is operative at a distance, independently of a coaggregation mechanism and therefore does not require any signals initiated by the activating receptors. In the case of FcαRI monomeric serum IgA transduce inhibitory signals through the FcαRI–FcγRIγ-chain complex [4]. The underlying molecular mechanism involves an initial very low intensity FcαRI activation step that promotes a Syk-dependent recruitment of the tyrosine phosphatase Src homology region 2 domain-containing phosphatase-1 (SHP-1) to the FcγRIy ITAM and the movement of FcαRI to lipid rafts. After raft recruitment both inhibitory and activating receptors and the inhibitory molecular effector (SHP-1) can be found in intracellular structures that we have called “inhibisomes”, which diminish Syk and ERK phosphorylation of the heterologous activating receptors and hence their function [5]. Therefore, similar to ITIM-mediated signals, down-regulation of the response of the heterologous activating receptor that is also recruited into rafts involves the association of inhibitory receptors with the tyrosine phosphatase SHP-1. The formation of inhibisomes also requires the SHP-1-dependent dephosphorylation of actin. Thus, both IgA-induced activating and inhibiting signals depend on FcαRI–FcγRIγ-chain ITAM, but differ in the recruitment of tyrosine kinases versus tyrosine phosphatases, respectively. As such, it has been proposed that the cross-linking of FcαRI during infection with IgA-opsonized pathogens results in proinflammatory responses, whereas naturally occurring serum IgA (which are not complexed with an antigen) induce inhibitory signals through the FcαRI, in order to dampen excessive immune responses [3]. These findings demonstrated that monomeric IgA treatment may also be beneficial to prevent or reverse an established inflammatory disease and thus it constitutes the basis for a future development of mIgAIV therapeutic approach.

Neutrophil FcR activation and ANCA

Human neutrophils express mainly three types of FcR, the FcγRIIA, the FcγRIIB and the FcγRI. It is interesting to note that FcγRIIA, is an activating single transmembrane receptor that...
contains an ITAM-like motif in its cytoplasmic tail. This is an unique activating receptor that lacks homology in the mouse. Moreover, FcγRIIB expressed by neutrophils lacks its trans-
membrane domain and it is linked to plasma membrane by
lipids (GPI anchor), and thus cannot alone activate the cell. 
Finally, FcαRII represents the only FcγR associated receptor on
resting neutrophils. In ANCA associated diseases, ANCA have
bound their neutrophil-expressed antigens, signalling and ac-
tivation are initiated through FcRs. Several investigators have
characterized the part of the ANCA molecule that is important
for neutrophil activation. ANCA Fc part seems important as
ANCA Fab did not trigger activation [6].
ANCA IgG bind to FcγRIIa (CD32A) and FcγRIIB (CD16B).
FcγRIIa blockade abrogated ANCA-induced activation,
whereas the role of the FcγRIIB blockade is somewhat more
controversial. The FcγRIIc has two allelic variants with either a
histidine or an arginine at amino acid position 131, resulting
in a high-responder and low-responder receptor form. Neut-
rophils with the high-responder variant showed a stronger
response to anti-PR3 and anti-MPO IgG1 mAbs in vitro. This
FcγRIIa has also good affinity to the IgG3 subclass, which is
the dominant ANCA subclass in patients with active disease,
and had the strongest capability to induce neutrophil adhe-
sion in vitro. ANCA IgG also bind to the FcγRIIB on neutrophils
that is expressed approximately 10 times higher than the
FcγRIIa. Distinct patterns of CD11b increase and CD62L shedding
suggested that FcγRIIa is involved in ANCA-induced
neutrophil activation. FcγRIIB has two common genetic var-
iants characterized by a single nucleotide polymorphism
(SNP) that changes the amino acid sequence in the coding
region. A serine (A) is associated with less inflammatory
cytokine release and a glycine (G) with more phagocytosis
and cell activation. IgA ANCA and the SNP variants of the FcγR
has been shown in GPA patient cohorts [7]. IgA ANCA were
present in 27% of the GPA patients, and were less frequent in
those patients who developed end-stage renal disease and
more frequent in those with upper airway manifestation [8].
The G allele was, however, found more frequently in patients
with renal disease and less frequently in those with upper
airway manifestation. Neutrophils with the proinflammatory
allelic FcγR1 variant triggered a stronger activation response
into IgG ANCA in vitro. Thus, the data indicate that FcγR and
FcγR1 genotypes influence manifestation patterns and dis-
ease severity in patients with ANCA-induced vasculitis. More-
ever, post-translational modifications such as sialylation
might be an additional mechanism to change the activating
capability of ANCA. It has been shown that the PR3–ANCA
sialylation ratio was significantly lower in patients with
active disease correlating with the Birmingham Vasculitis
Activity Score (BVAS) score. Moreover, the in vitro respiratory
burst was correlated inversely with sialylation of the PR3–
ANCA IgG.

Conclusions
All these findings suggest an important interplay between
the ANCA antigen-binding fragment, the Fc part with its isotype
and class characteristics and post-translational ANCA modifications
as well as important genetic variants in the corresponding Fcα
and Fcγ receptors on the neutrophil that may determine the
mechanisms and strength by which ANCA interact with the
neutrophil.

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