Results: Neutrophils stimulated with IFNs in vitro underwent rapid phosphorylation of STAT proteins (5–30 min). Addition of IFNs to neutrophil suspensions containing GM-CSF or TNFα had a profound dose-dependent effect on the function of the inflammatory cytokines. Type-I IFNs abrogated the protective effect of GM-CSF on neutrophil apoptosis at 18h (GM-CSF 15.6% ± 2.7, GM-CSF + IFNγ 39.5% ± 1.2, P < 0.01), whereas Type-II IFNs enhanced the anti-apoptotic effect of TNFs (TNFα 52.3% ± 3.3, TNFα + IFNγ 27.4% ± 1.2, P < 0.05) and sustained the TNFs priming effect on the respiratory burst for up to 4h (P < 0.01). Type-I and Type-II IFNs enhanced STAT3 phosphorylation by GM-CSF, and altered the activation kinetics of ERK and AKT by GM-CSF. Type-I IFN enhanced AKT phosphorylation in TNFα stimulated neutrophils.

Conclusion: IFNs profoundly alter the functional effects of inflammatory cytokines on neutrophils in vitro. This may have important consequences in vivo during therapy with biologic drugs such as TNFα. The complexity and heterogeneity of inflammatory diseases such as RA, where different cytokines dominate or act synergistically to perpetuate systemic inflammation, may explain why some patients respond better to certain biologic therapies than others. We are currently investigating the consequences of TNFi (Infliximab) and JAKi (Tofacitinib) on neutrophils stimulated in vitro with IFNs, GM-CSF and TNFα.

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