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Interferon-γ-induced necrosis: an antitumor biotherapeutic perspective.

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Abstract

Interferon (IFN)-γ-like the well-known antitumor biotherapeutic IFN-α-is a powerful antiproliferative and immune modulatory cytokine, but mixed results from clinical trials, together with issues of systemic toxicity, have dampened enthusiasm for its use in the treatment of cancer. We suggest that at least 2 factors reduce the antitumor efficacy of IFN-γ: (1) poorly understood survival mechanisms that protect most tumor cells from IFN-γ-induced direct cytotoxicity, and (2) the short half-life of IFN-γ in serum. In this review, we outline avenues to overcome both these limitations. First, we have identified the transcription factor nuclear factor-kappa B (NF-κB) as a protective mechanism against IFN-γ-induced necrosis, and disabling NF-κB allows IFN-γ to trigger RIP1 kinase-dependent programmed necrosis (or necroptosis) in otherwise resistant cells. Second, we propose that fusing IFN-γ to tumor-specific antibodies will stabilize IFN-γ in serum and target this cytokine to tumor cells. We expect that such IFN-γ-antibody chimeras (called immunocytokines), when combined with agents that neutralize tumor-intrinsic survival signals such as NF-κB, will exert potent tumoricidal activity with minimized systemic side effects. Although this review will focus on exploiting IFN-γ-induced necrosis for treatment of renal cell carcinoma, these approaches are also directly applicable to several human cancers in which IFNs have shown therapeutic potential.

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