

## MINI-REVIEW

# Potentials of interleukin-27 (IL-27) as an immunotherapeutic cytokine in cancer therapy

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## ABSTRACT

Cancer immunotherapy using cytokines has been sought as an alternative therapeutic approach for treating cancers. Besides remarkable immunoregulatory properties, interleukin (IL)-27 has recently been shown to possess promising anticancer functions; hence, its potential roles in cancer immunotherapy. Although proven to be effective against cancer cell growth and angiogenesis, given its dual immune-regulating functions (pro-inflammatory and anti-inflammatory), the use of IL-27 as a cancer immunotherapeutic cytokine could possibly be a two-edged sword without meticulous and thorough research. This mini-review mainly discusses the functions and future prospects of IL-27 as an effective anticancer cytokine. Hopefully, it imparts useful insights into the potential applications of IL-27 in cancer immunotherapy

**Keywords:** interleukins; IL-27; cytokines; immunotherapy; cancers

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## Introduction

Given various detrimental side effects of modern anticancer treatments, cytokine immunotherapy has been sought as an alternative therapeutic approach. A combinatorial immunotherapy of interleukin (IL)-12 with a breast cancer-specific monoclonal antibody, trastuzumab and an anticancer drug namely paclitaxel was found to inhibit breast cancer cell growth as high as 52% in the first-phase clinical trial<sup>[1]</sup>. However, repeated administration of IL-12 did somehow render toxicity to metastatic kidney cancer and breast cancer patients<sup>[2]</sup>. As a result, to optimize the use of cytokines in cancer immunotherapy, scrupulous research on therapeutic cytokines especially those capable of triggering both pro-inflammatory and anti-inflammatory reactions is undoubtedly entailed. In this mini-review, the anticancer functions of IL-27, with pro- and anti-inflammatory effects, and its future prospects in cancer immunotherapy are highlighted.

## Interleukins are more than just immune modulatory cytokines

Interleukins (ILs) have long been recognized for their immune modulatory functions such as regulating local and systemic immunity by controlling immune cell proliferation, differentiation and motility. By doing so, immune homeostasis is achieved between pro- and anti-inflammatory reactions<sup>[3]</sup>. In the recent decades, the potentials of ILs have been further explored and found effective as immunotherapeutics against various cancers. ILs such as IL-2 has been approved by US Food and Drug Administration (FDA) for use in cancer immunotherapy, for instance in treating metastatic melanoma<sup>[4,5]</sup>. Besides IL-2, IL-12 was also found to exhibit direct inhibition on cancer cell growth while promoting activation of immune cells with cancer killing functions<sup>[2]</sup>. The anticancer properties of IL-12 were well observed in various

maglinant models such as B16 melanoma, breast ductal adenocarcinoma, C26 colon carcinoma and metastatic lung carcinoma<sup>[6]</sup>.

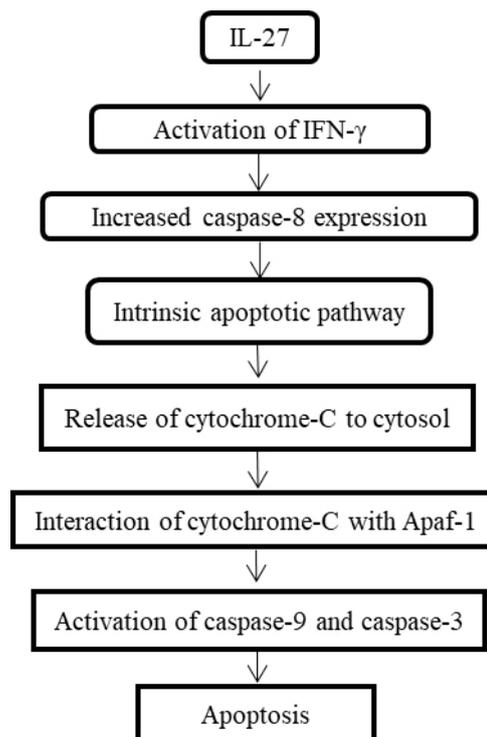
Although proven with prominent anticancer functions, IL-12 immunotherapy was, however, reported to render adverse side effects such as hypersplenism in melanoma patients<sup>[7]</sup> which in turn results in extravascular hemolysis and enlargement of spleen. To overcome the adverse effects, IL-27, which is also a member of IL-12 family, has been merited for its antitumor benefits without causing much adverse toxic effects in cancer models<sup>[4]</sup>. Of note, IL-27 could be harnessed as an alternative anticancer cytokine in cancer immunotherapy<sup>[8]</sup>.

IL-27 is composed of Epstein-Barr virus-induced gene-3 (EBI-3) and p28 subunits that interact with cell receptors that are made up of WSX-1 and gp130 subunits<sup>[9]</sup>. IL-27 is often produced by antigen presenting cells and particularly important in T-cell proliferation. IL-27 functions as both pro- and anti-inflammatory cytokine, for instance, it promotes Th1 responses but inhibits proliferation of Th17 that is responsible for many inflammatory reactions<sup>[10]</sup>. As a result, the use of IL-27 as a therapeutic agent entails scrupulous and rigorous investigation so it does not produce undesired outcomes in recipients. This is particularly crucial in cancer therapy as any agents that generate excessive inflammation would cause drug resistance and metastasis in cancers<sup>[10]</sup>.

### Inhibitory functions of IL-27 on cancer cells

To better employ IL-27 as an immunotherapeutic cytokine for cancers, the mechanisms of actions on how IL-27 exerts its anticancer functions have to be unraveled. As an immunoregulatory cytokine, IL-27 signals activation of natural killer (NK) and cytotoxic T cells which possess cancer killing properties<sup>[11]</sup>. Besides regulating antitumor immune responses, IL-27 has also been proven to execute direct inhibitory functions on cancers. For instance, inhibiting pediatric B-acute lymphoblastic leukemia cell proliferation<sup>[12]</sup>, prohibiting angiogenesis in melanoma B16F10 cell line and blocking metastasis of lung cancer in mouse model<sup>[13]</sup>. Inhibition of metastasis of lung cancer by IL-27 is mostly attributed to suppression of cyclooxygenase-2 (COX-2)<sup>[14]</sup> and downregulation of epithelium-mesenchymal transition (EMT) in lung cancer cells<sup>[15]</sup>.

Apart from the aforementioned antitumour activities, cancer cell death *via* apoptosis is often targetted by many antitumour agents. Antitumour agents with apoptotic properties trigger mitochondrial oxidative stress which then results in the release of cytochrome-C, activation of caspase cascade and eventually cell death<sup>[16]</sup>. Ruiz-Ruiz *et al.*<sup>[17]</sup> showed that IL-27 was able to trigger apoptosis in breast cancer cells by stimulating interferon (IFN)- $\gamma$  expression. Activation of IFN- $\gamma$  subsequently increases the expression of pro-apoptotic protein, caspase-8 in MCF-7 and MDA-MB-231 breast cancer cell lines. Through caspase-8 activity, the intrinsic pathway is activated and cytochrome-c is released and interacts with protease activating factor-1 (Apaf-1) which in turn promotes caspase-9 and caspase-3 activation and apoptosis (**Figure 1**). Collectively, the immunoregulatory, direct inhibitory and apoptosis-promoting functions of IL-27 add up to its potentials as an immunotherapeutic agent.



**Figure 1.** Activation of apoptotic protein cascade by IL-27. Through activation of IFN- $\gamma$ , IL-27 is able to induce apoptosis in breast cancer cell lines.

### Future prospects of IL-27 in cancer immunotherapy

IL-27 is unequivocally a prominent immunoregulatory cytokine that promotes both pro-inflammatory and anti-inflammatory responses. In order to avoid treatment outcomes that could

encourage metastasis and drug-resistance in cancers which in turn undermine an anticancer therapy regime<sup>[10]</sup>, any claims on the potential use of IL-27 as an immunotherapeutic cytokine should be preceded by meticulous and rigorous experimentations. Anticancer functions of IL-27 can be further explored by (a) detailed investigation on the ability of IL-27 in promoting NK cells and tumor-specific T cell proliferation *ex vivo* and how these activated cells target tumors in adoptive cell therapy; (b) expanding the IL-27-induced apoptosis networks in cancer models. With great breadth of understanding on how IL-27 effects anticancer functions in cancer cells, this ensures more precise use of IL-27 as an immunotherapeutic agent without causing much damaging side effects to cancer patients. As a conclusion, IL-27 does hold prominent potentials in cancer immunotherapy. Rigorous empirical evidence would be able to help further unveil its importance in cancer immunotherapy.

## Conflict of interest

The authors declare no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

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