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Review

The role of IL-7 in Immunity and Cancer

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Abstract. *Interleukin-7 (IL-7) is a cytokine that has been known since long in immunology, mainly regarding its effects on T-cells and B-cells. IL-7 has been demonstrated to be necessary for both B-cell and T-cell proliferation and lack of IL-7 causes immature immune cell arrest. Interestingly, in recent years, certain studies have strongly suggested that the role of IL-7 is far beyond the field of immunology, it might have direct or indirect effect on cancer. This review aims to summarize the role of IL-7 in immunity and its role in the pathogenesis of neoplasia.*

Interleukin-7 (IL-7) was discovered in 1980s. It is one of the members of IL-2 superfamily (1). IL-2 superfamily includes IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21. It binds to receptors with a common γ chain subunit (2-4). In addition to a common γ chain subunit, the receptor for IL-7 (IL-7R) requires an IL-7R α chain in order for binding to take place. Due to the frequency of the common γ chain subunit, the presence of the IL-7 receptor α chain is a better identifier for when IL-7 will actually bind to a receptor. IL-7–receptor binding results in phosphorylation of tyrosine residues on the receptor. This leads to activation of JAK1 or JAK3 depending on the cell type, which later activates many downstream signaling pathways including STAT5a/b, PI3 Kinase, and SRC kinases as shown in Figure 1 (2-6). It is well-known that IL-7 plays a critical role in the development of B-cells and T-cells (7). In recent years, increasing evidence suggests that IL-7 may also play a pivotal role in the pathogenesis of neoplasia. This review will highlight the updated information regarding the role of IL-7 in immunity and cancer.

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The Role of IL-7 in the Development of B-cells

IL-7 has been found to play a critical role in the development of B-cells. While not directly due to IL-7, there seems to be some relation between IL-7 and the pre-B-cell receptor in the survival, proliferation and differentiation of B-cells (8-10). This relationship should be further examined, as current models demonstrate IL-7 not being required for human B-cell development (11) despite its necessity in mice models (12). In relation to B-cell development in neonates, there appears to be a strong effect of increasing B-cell proliferation in cord blood $CD34^+$ cells when exposed to IL2 and IL-7 (8-10). Administration of IL-7 to normal mice leads to an increase in pre-B-cells and mature B-cells (13-15). Administration of IL-7 to lymphocyte deficient mice leads to an increase in mature B-cells (8-10).

These B-cell-promoting effects of IL-7 are seen in stark contrast to some effects that appear to promote B-cell apoptosis. $CD95^+$ B lymphocytes generally are associated with HIV1 infection. Current treatments sometimes involve some regiment of IL-7. However, it appears that IL-7 induces the apoptosis of these $CD95^+$ B-cells (16). In addition to these pro-apoptotic effects, IL-7 also appears to stunt B-cell maturation in HIV infected patients. This was demonstrated by a marked increase in these immature B-cells when given an administration of IL-7 (17). These effects of IL-7 on immature B-cells does not come necessarily as a surprise. Human pre-B-cells do have IL-7 receptors and respond to IL-7 when presented in the presence of stromal cells (18).

Additionally, IL-7 can act as a trophic factor in many developing B-cells. BCL2 family members and certain membrane proteins have been shown to have a role in this effect, however, the exact mechanism is still unclear (19).

IL-7 also works with stromal derived factor1 (SDF1), stem cell factor (SCF), and fms-related tyrosine kinase 3 ligand (FLT3LG) in order to regulate B-cell development (20-22).

Mature B-cells are usually unable to respond to IL-7, however, a small group of peripheral B-cells have been shown to be responsive. *In vitro* studies have demonstrated that B-cell receptor antigen diversity occurs during development, but further changes can happen, and are controlled by recombinase-activating genes (20-22). Oddly enough, *in vitro* generation of B-cells did not require IL-7 at all, despite the overwhelming amount of evidence that IL-7 is required for B-cell maturation *in vivo* (23, 24).

The Role of IL-7 in the Development of T-cells

T-cell development occurs through several stages in the thymus. Immature T-cells need to reach sufficient levels because their development has several stages known as positive and negative selection, contributing to the loss of 98% of T-cells (25). In relation to T cell development in general, triple negative precursors migrate into the thymus where they mature. As they mature, they go through the cortex into the medulla, and it is from here that the single positive T-cells leave to enter the circulation. The thymus is the primary location of T-cell production although T-cells have also been shown to develop in the intestine, aided by IL-7 (26). This development of T cells is also supported by *in vitro* studies. Where regulation of human T cell maturation was achieved by decreasing IL-7 and increasing anti-CD3 levels (27). These effects are supported by studies demonstrating how intrathymic T cell development is dependent in some part on the presence of IL-7 (28). Specifically, IL-7 along with thymic stromal lymphopoietin seem to be necessary for Treg maturation (29).

Similar to B-cells, T cell maturation seems to be stunted by IL-7 in HIV infection women. This has been demonstrated in patients both before HAART treatment and after. This effect seems magnified when patients are coinfected with HCV, as HCV seems to increase circulating IL-7 (30). Oddly enough, this is in contrast to other data suggesting IL-7 restores T cell diversity (31). Both studies were performed on HIV positive patients and done in recent years. As a result, further studies on the matter need to be conducted.

IL-7 has been demonstrated to enhance thymocyte viability (32, 33). IL-7 has anti-apoptotic effects which involve BCL-2 associated X protein (BAX) which is part of the BCL-2 gene family (33). B-cell lymphoma 2 (BCL2) has also been shown to decrease in IL-7 deficient mice, which later caused increased apoptosis (34). Additionally, BCL2 transgene expression in IL-7R deficient mice resulted in restoration of mature T-cells (35, 36). This data indicates the regulatory role IL-7 plays in apoptosis *via* changes to the BCL2 family.

IL-7 appears to be necessary for proper T-cell receptor γ locus rearrangement, although IL-7 involvement in other locations is unclear. It appears as if the regulation of this rearrangement occurs through STAT5 histone acetylation (37, 38).

Potential Anti-tumor Effects of IL-7

IL-7 presents antitumor effects in tumors such as glioma, melanoma, lymphoma, leukemia, prostate cancer, and glioblastoma. In vivo administration of IL-7 resulted in a decreased cancer cell growth in murine models. Additionally, the same study demonstrated that graft *versus* tumor action was promoted in models if the graft is an allogeneic graft that is first T-cell replete (38). This data supports the concept that IL-7 has antitumor properties. IL-7 has been shown to enhance the antitumor effect of interferon-γ (IFNγ) in rat glioma tumors (39). IL-7 can also induce the production of IL-1α, IL-1β, and TNF-α by monocytes. These cytokines promoted IL-7 seem to help inhibits melanoma growth (40). IL-7 also appears to limit lymphopenia-induced proliferation (40). It has also been demonstrated to have a confirmed anti-tumor immune response. IL-7 has been demonstrated to be the most effective cytokine in increasing cytotoxic CD8+ T lymphocytes ($CD8^+$ T-cell) when compared to IL-2 and IL-4 (41). It has been demonstrated that long-term tumor antigen specific $CD8^+$ T-cell responses are enhanced by IL-7 treatment (42). Prevention of mutation to IL7Rα is of vital importance for preventing leukemia. Namely, it has been demonstrated that a gain-of-function mutation to results in an oncogenic function of the receptor. As a result, an increased propensity of T-cell acute lymphoblastic leukemia occurs (43). These findings suggest that IL-7 can enhance lymphocyte response within tumors.

Prostatic acid Phosphatase (PAP) was fused into various cytokines, including IL-7. In an *in vivo* study, simultaneous intraperitoneal administration of PAP-fused IL-7, GMCSF, IL-2, and IL-4 resulted in a decreased induction and growth in PAP expressing tumors. This finding suggests that IL-7 in addition to these other cytokines has an antitumor role in prostate cancer (44). The CD47 gene is over expressed in several tumors including glioblastomas. The over-expressed CD47 in many tumors seems to help control tumor growth by increasing expression of IL-7 (45).

After treatment of pediatric sarcomas, immune response is often deteriorated. However, treatment with recombinant human IL-7 as an adjuvant therapy seems to promote immune recovery, as measured by CD4 count recovery (46). Increasing IL-7 responsiveness by increasing IL7Rα levels seem to also promote antitumor immunity (47). There is some suggestion that higher T-cell survival could by linked with better antitumor function that is durable. Recent studies have demonstrated that preinfused T-cell clones that possess IL-7R and c-myc are more likely to persist in patients (48). There appears to be great antitumor effect in chimeric IL4

and IL-7 exodomain fusion. This is a newer treatment, so generation of it as such still requires future clinical trials (49). The antitumor effects of IL-7 does seem to include simply increasing proliferation and antitumor activity of IL-7α (50). It has been shown that adjuvant IL-7 treatment improves antitumor functions in animal models and this seems to be mainly due to an increased IL-6 as well as a magnified Th17 differentiation (51). Finally, it is of interest that IL-7 administration in GMCSF-secreting tumor mice greatly prolonged their survival (52). Thus, IL-7 seems to have an anti-tumor effect in a direct or indirect manner.

Potential Pro-tumor Effects of IL-7

Interestingly, besides the studies suggesting that IL-7 might have a potential anti-tumor effect, some other studies indicate that IL-7 might also have potential pro-tumor effects. There does appear to be effects IL-7 has on preventing apoptosis by regulating the BCL2 gene family, namely BCL2 Associated X protein (BAX), in lung cancer and thus promoting its proliferation. However, its exact effects on non-small cell lung cancer is still unclear (53). Additionally, IL-7 appears to promote bladder cancer invasion & migration *via* limitation of p27kip (54). The IL-7R gene appears to be an oncogene that is mutated in T-cell acute lymphoblastic leukemia, (43). Future studies are needed to understand the role of these mutations and their effects on cancer.

One study suggests that IL-7 has an important role in the prevention of apoptosis (53). IL-7 and IL-7R induce up-regulation of cyclin D1 is required for progression through the G_1 phase of the cell cycle. When tumors are present, cyclin D1 expression increases and leads to greater quantities of cells entering G_1. Significant decrease in cancer cell apoptosis has been shown resulting from the activation of IL-7 and IL-7R. Similarly, qPCR assays have shown increases in the level of anti-apoptotic BCL2 accompanied by the decrease in pro-apoptotic p53, and a down-regulation of BCL2 Associated X protein. Besides the effect of IL-7 on prevention of apoptosis, IL-7 may also promote cFOS and cJUN activity in cancers such as non-small cell lung cancer (55). Activation of cFOS and cJUN will in turn accelerate proliferation of cells and increase lymphovascular formation (55). Thus, IL-7 seems also to have a potential tumor-promoting effect.

Conclusion

In this review, the main developmental signaling pathways of IL-7 were discussed, accompanied by the roles that IL-7 may play in immunity and pathogenesis of neoplasia. Since cytokine-based immunotherapy plays an important role in the treatment of advanced malignant tumors, such as renal cell carcinoma and melanoma, it is necessary to expand our understanding of the role of cytokines, such as IL-7, in the pathogenesis of neoplasia. The role of IL-7 in the pathogenesis of neoplasia seems controversial. A possible explanation for the conflicting evidence found in the literature is that cytokines are found in different levels of balance based on their physiological location, with the degree of neoplastic progression also resulting in differing cytokine expression. Clearly, further intensive studies are needed to elucidate the contexts in which IL-7 functions as a tumor promoter *versus* as a tumor inhibitor. We are looking forward to the development of safer and more effective cytokine-based immunotherapy to benefit patients with advanced malignancy.

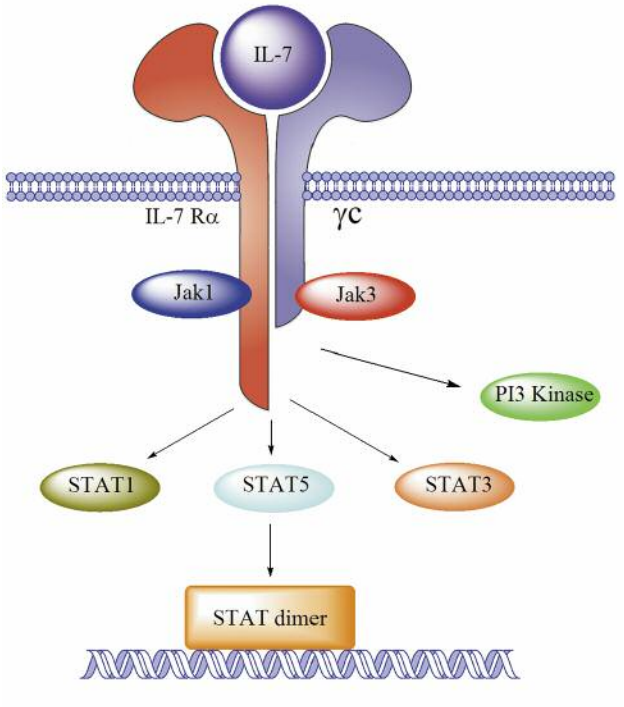

Figure 1. *IL-7 signal pathway.*

Conflicts of Interest

The Authors have no conflict of interest.

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