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PERTURBATIONS OF IL-10 LEVELS IN THE HYPOPHARYNGEAL CANCER: AN UPDATE

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ABSTRACT

Hypopharyngeal cancer (HPC) is a disease in which malignant cancer cells accumulated in the tissues of the hypopharynx. Certain viruses are known to exert a significant impact on hypopharyngeal carcinogenesis; however, numerous other factors thought to influence its tumor proliferation and metastasis. Among numerous factors, Interleukin 10 (IL-10) is a prominent anti-inflammatory agent known to evade the immune system via an immunosuppressive condition. Role of IL-10 in the neoplasm is still debatable and inadequately comprehended, but it is one of the many cytokines involved in the growth and maintenance of cancer.

In the present review, we explored and highlighted the dual role of IL-10, its secretion level in HPC sufferers, and its role in metastasis and development. We examined the literature focusing on the research that looked into the IL-10 secretion level in the serum and tissues related to the HPC individuals. The advanced clinical stage of hypopharyngeal neoplasm is on the rise and concurrently associated with IL-10 levels. The existing research on IL-10 related to HPC showed differential effects and hence, no clear inference can be attained. The discrepancies observed could be related to variations in sample selection-plasma, tissue, or serum, and differences in assays, variable stage of cancer, comorbidities etc. Although, the higher likelihood of IL-10 detection linked to more advanced tumor stages does imply that the tumor is at least partially attributable to the IL-10 perturbations. This finding still has to be verified by prospective studies on cancer patients in various stages, but the available data are convincing enough to support a viable working theory.

KEYWORDS: Hypopharyngeal cancer, Cytokine, IL-10 · metastasis.

INTRODUCTION

Hypopharyngeal cancer (HPC) is a rare type of malignancy, that affects > 5 percent of all head & neck squamous cell carcinomas (HNSCCs) (1). Histologically, the hypopharynx is a diverse sub-site within the head and neck region that includes the pyriform sinus, post-cricoid, and posterior pharyngeal wall (2,3). However, owing to its assertive nature and covert positioning, 70-80% of cases of HPC are discovered at a severe stage (1,4). Significant advances in therapeutic modalities have been introduced, still, the probability of surviving five years is around 50% (4–7). Cigarette smoking and alcohol drinking are notable indicators of risk for HPC (5,8,9). Numerous studies also suggested involvement of viruses such as the HPV & EBV in the genesis of cancer in this location. The studies revealed that different rates of cancer disease development are caused by genetic abnormalities brought on by oncogenic viruses. The varying levels of cytokines and numerous other growth factors are responsible for this outcome (10). These anomalies influence the development of metastases as well as the rate of cancer progression. (10).

While it is known that cytokines found in the microenvironment of tumour can suppress cell proliferation, HNSCC cells have evolved molecular defences against this impact (7). Therefore, a changed response to cytokine stimulation is significantly linked to the malignant transformation process in HNSCC. The aggressiveness of cancer, how it responds to chemotherapy and radiation treatment, and how it affects immune system cells are all significantly influenced by changes in immunological, inflammatory, and angiogenic reactions within the HNSCC microenvironment.

Nearly all immune cells, both innate and adaptive, release soluble substances called cytokines (11). These are released when cytokine-producing cells are triggered. These activated cytokines regulate a wide range of cellular processes by binding to specific cytokine receptors on different cells (11). T helper 1 (Th1) & T helper 2 (Th2) cytokines are two different types of cytokines that have been classified. Th1 cytokines promote cellular immunity to eliminate intracellular invaders such as viruses and cancerous

cells. While Th2-type cytokines control humoral immunity by encouraging the creation of antibodies to fight pathogens outside of the cell. The Th1/Th2 balance may provide insight into how the immune system eliminates tumors and infectious pathogens. In general, it has been demonstrated that immune responses in cancer patients are predisposed to the generation of Th2-type cytokines, which limits the formation of an effective anti-tumor Th1 immune response. Additionally, patients with HNSCC have been found to have lower amounts of Th1-type cytokines. The principal cytokines found in the microenvironment of the HNSCC include IL-4, IL-6, IL-8, IL-10, vascular endothelial growth factor (VEGF), granulocyte-macrophage colony-stimulating factor (GM-CSF), prostaglandin E2 (PGE2), and basic fibroblast growth factor (bFGF) (7,11). Considering that IL-10 is a significant cytokine with significant anti-inflammatory and immunoregulatory capabilities, its genetic variants may have an impact on the immune system of the host, HPV infection, and, eventually, the HPV status and prognosis of individuals with hypopharyngeal carcinoma (12). It is involved in the feedback regulation of Th1 cells (13,14). Numerous studies have revealed that many viruses specifically target IL-10 to affect the human immune system. (15). A vicious cycle characterizes the relationship between IL-10 and HPV, in which IL-10 promotes the expression of several early HPV proteins (such as E6 and E7) while A few HPV proteins, including E2, E6, and E7, also stimulate IL-10 expression. In various malignancies, increased serum IL-10 levels have been documented (13). Elevated serum levels could potentially be related to the disease's stage. Increased IL-10 expression in HPC has been associated with inhibition of the anti-tumor T cell immune response, allowing cancer to escape. Additionally, the interaction of IL-10 with cytokines – VEGF, IL-1β, TNF-α (Tumor necrosis factor- α), and IL-6 to modulate cell activities has been reported in several studies (12). The immunosuppressive actions of IL-10 in the neoplastic environment have been consistently proven in the oropharynx and many other places, but no definite conclusion has been obtained in the hypopharynx (10). In this review, we present the dual role of IL-10, its secretion level in HPC sufferers, and its role in metastasis and development.

The Paradox Role of IL-10 in Genesis Of Carcinoma

The pleiotropic cytokine IL-10 can influence inflammation and immunological control in the setting of both innate and adaptive immunity. Despite being classified as a Th2-type cytokine, IL-10 is now known to be generated by a diverse spectrum of cell types (13). Myeloid and lymphoid lineaged cells are associated with the release of Il-10 as a response to various stimuli (15). Of this monocytes and regulatory T cells (Treg) are the principal sources of IL-10, while other cells mediating suppression, such as tumor cells, also generate it (13). IL-10 interacts with the cell surface Interleukin-10 receptor. It pertains to the class II cytokine receptor family and is found in many different types of cells, including thymocytes, T cells, B cells, NK cells, monocytes, and macrophages. IL-10 is usually thought to be an anti-inflammatory or immunosuppressive factor that contributes to immunological tolerance. But there is disagreement concerning the function of IL-10 in controlling the immune system. Cells including mast cells, macrophages, neutrophils, NK cells, T and B lymphocytes, myeloid-derived suppressor cells, and DCs make up the tumor microenvironment (13). Moreover, activated immune effector cells are available in both the tumor and the blood of cancer patients. Yet, immune responses to cancer appear to be defective and tumor progression occurs despite apparent immunological activity (13). Consequently, IL-10 is widely thought to be released by tumors (or tumor-infiltrating immune cells) that help malignant cells to evade immune surveillance (13,15). Several studies have linked up the overexpression and administration of IL-10 with tumor shrinkage and rejection (15). Also, the activity of DC and macrophages is slowed down by IL-10 (13). As a result of its suppressive properties, the production of MHC class II, co-stimulatory molecules and the release of pro-inflammatory (Th1) cytokines are also inhibited. IL-10 down-regulates the secretion of IFN-γ and IL-2 by antigen-presenting cells (APC) (7,13). As a result, the antigen processing system and the APC's ability to present tumor-associated antigens are suppressed. A build-up of MHC I molecules in the endoplasmic reticulum is caused by IL-10's down-regulation of TAP1 and TAP2 expression. It guards against the cytotoxicity caused by cytotoxic T-lymphocytes (CTL).

Additionally, IL-10 plays several mechanisms in mediating anti-tumor action. It stimulates NK cell activity, that assists in cancer cell eradication. It may increase the release of antibodies from harmed cells, and it prevents APCs from maturing, which increases their capacity to take up antigens and keep them in place rather than travel to nearby lymph nodes. Through the induction of metalloproteinase (MMP) inhibitors, IL-10 also reduces tumor angiogenesis and invasiveness. Furthermore, as chronic inflammation is strongly linked to the development and progression of tumors, the anti-inflammatory property of IL-10 may result in the reduction of tumor growth. IL-10 also suppresses NF-B

activation, preventing the generation of proinflammatory cytokines. Through its anti-inflammatory properties, it might cause tumors to shrink.

METHODS

Several research examining the relationship between IL-10 polymorphism and HPC have already been reported. Data on the cytokine profile of IL-10 level in HPC, however, are still lacking. As a result, pieces of information from the literature that examined the level of IL-10 secretion in head and neck carcinoma—including the hypopharynx site—were included in this investigation. Published studies were extracted from PUBMED and Google Scholar.

MAJOR INSIGHTS

Within the tumor microenvironment, IL-10 is known to promote immune suppressive activities. Notably, several studies suggest that the immune responses in HPC patients are skewed in favor of Th2 cytokine release, which is considerably known to suppress the anti-tumor immune responses of Th1. Accordingly, Chen et al. (4) discovered expression levels of Th1, Th2, and Th17-associated cytokines in peri carcinoma and hypopharyngeal cancer tissues in 53 HPC patients and 7 patients with throat injuries acting as controls. They claimed Th2 cytokines promote tumor progression, which was corroborated by the discovery that HPC tissues consistently expressed considerably higher levels of IL-4, IL-6, and IL-10 mRNA than peri carcinoma tissues at all clinical stages. In addition, Jebreel et al. (16) investigated alterations in IL-10, IL-12, and IL-18 in HNSCC patients in comparison to non-tumor controls. In their study, fifty-six cases with primary HNSCC (including 10 HPC patients) and 40 non-tumors were enrolled. In comparison to non-tumor controls, they found that the IL-10 in serum was significantly higher in the HNSCC patients. Additionally, there was a discernible difference between the prevalence of IL-10 detectability in tumors from various sub-sites; IL-10 detectability was more prevalent in tumors of the hypopharynx and less prevalent in oral cavity cancer. Alhamarneh et al. (6) reached a similar outcome in their investigation. In contrast to the oral cavity tumors, which demonstrated the opposite, there was a significantly enhanced probability of noticeable IL10 levels in the larynx, oropharynx, and hypopharynx. Inconsistent findings have been reported by prior investigations on the circulating cytokines in HNSCC. Pries et al. (11) examined an HNSCC cell line devoid of tumor-invading immune cells and discovered elevated levels of the tumor-inducing cytokines IL-6 and IL-8 but low levels of the immune suppressive cytokine IL-10. In research including twenty four patients of HNSCC and 28 controls, Riedel et al. (17) reported that serum levels of IL-18 enhanced while IL-10 and IL-12 levels remain unaltered. This is at odds with the great majority of reports that have been released. The discrepancies observed in these studies could be possibly due to variations in sample selection-plasma, tissue, or serum, and differences in assays.

CONCLUSION

In this review, the data of IL-10 perturbations are seemed to be associated with HPC, however many studies are conflicting, and hence, no clear interpretation can be realized. Although, the higher likelihood of IL-10 detection linked to more advanced tumor stages does imply that the tumor is at least partially attributable. This finding still has to be verified by prospective studies on cancer patients in various stages, but the available data are convincing enough to support a viable working theory.

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