



Interleukins and Cancer metastasis –A brief relation

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1. Abstract:

The word cancer mainly related with uncontrolled cell division and with altered cellular characters. It is well known to us that cancer is the most common and deadliest among all diseases. The syndromes and failure of several organs due to cancer metastasis cause death of most of the peoples in all over the world. Recent data suggest that in case of cancer metastasis immune cells play one of the major role rather than other factors. Among all immune cells the dendritic cells, Neutrophils and Inflammatory compounds are the forefront of this issue. Recent data suggest that the soluble cytokines that produced by the host or cancer cell, and by immune cells promote tumor growth along with invasion. As there so many types of interleukins (IL), those are responsible for the cancer progression this area is very important for cancer treatment by using various drugs. So here in this mini review we gather knowledge by considering only Interleukins and its roles in cancer metastasis. This paper deals with about the interleukins, their expression and role in cancer. This study will open a new way in cancer treatment.

Key-Words: Interleukins types, Metastasis, Treatment of Cancer, soluble cytokines

2. Introduction:

The role of the immune system in reacting to tumor tissue has been described as early as the eighteenth century [26]. Then comes the knowledge of Immune cells along with a novel approach to overcome the deaths of cancer that is known as cancer immune therapy. The goal of cancer immunotherapy is to overcome tumor-induced immunosuppression and augment an individual's own anti-tumor immune response using various strategies [27]. The cancer is reported second most common disease that causes large number of death [25]. As all different types of cancer have diverse special features, in this present day it is very hard for the modern science to cure this. It is reported that from primary site of cancer, immune cells help in cancer metastasis that is the main cause of secondary tumor growth. The tumor microenvironment that is composed of adaptive and innate immunity, related with cancer progression and its development [28]. Recently it is discovered that the cytokines are not only produced by host cells, cancer cells also can produce some of IL [30], and its related receptors to escape immune attack [29]. Due to this reason scientists are focusing this area to develop potential drugs or inhibitor that could help to increase host immune system along with prevent cancer.

3. About Cytokines:

These are biomolecules that are immune modulators, are responsible against infectious diseases and even tumor genesis by promoting its growth, tissue renewal etc [31]. In brief cytokines are main part of microenvironment by using them researchers combat cancer and by understanding their function, expression developing anti-cancer drugs [30]. IL are proteins that belong to superfamily cytokines. They are mediated intracellular signaling including cell proliferation, adhesion, migration of immune cells that's are very important for the inflammatory response. [32]. IL, to date, about 38 different interleukins have been identified, each binding to a unique type of receptor, having a specific origin, structure, and properties has both acute and chronic function. [31]

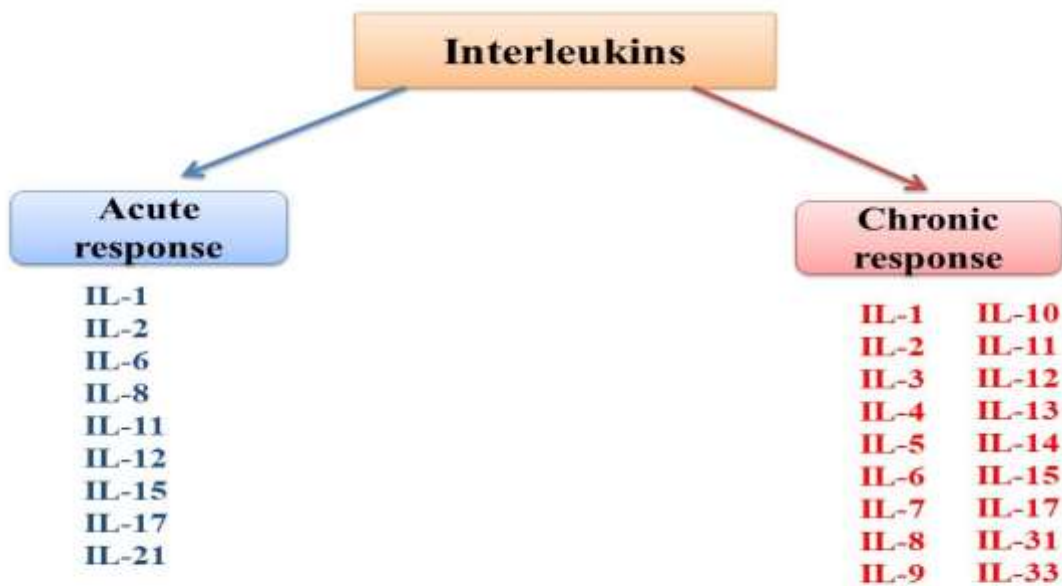


Fig.1. Interleukins involved in acute and chronic inflammatory responses [31,30].

4. Roles of Interleukins in Cancer:

The intra and extracellular communications in the vertebrate are controlled by cytokines.[1] In metastasis different cell signalling pathways are involved, such as integrin pathway, transforming growth factor (TGFB) beta pathway and other cytokines pathways. Interleukin 1 is an important cytokine that promotes tumour growth, angiogenesis and cancer metastasis. In a study of DM Elaraj *et al*, it has been shown that most of the metastatic neoplastic cells are positive to IL1[2]. In Cancer metastasis IL1Ra, IL8 and VEGF are also important. IL1Ra inhibit the xenograft growth of IL1 but it doesn't have any effective anti-proliferative actions. [2] IL1 alpha and IL1 beta have performed important roles. Induced IL1 alpha and IL1 beta works mostly same and acts on same receptor [3] but their forms are different. IL1beta are secreted form & IL2 alpha are only active in cell associated form. IL1beta and TNF are related to breast cancer metastasis. There are two inflammatory chemokines are CCL2 and CCL5. With this two types of chemokines and TNF alpha and IL1beta expressed in the cells are related to cancer metastasis and mostly in breast cancer metastasis[4]. In metastatic breast cancer cells IL1alpha and IL1B was positive, It was observed that in CD44+/CD22- breasts cancer cells invasion related genes like IL1, IL6, IL8 was positive which signifies the metastatic effect and the severity of the metastasis of those breast cancer [5,6]. Lin and Pollard *et al* study have shown that the macrophages in the primary mammary adenocarcinomas regulate late stage carcinogenesis by virtue of their proangiogenic properties[7], and the metastasis behaviour is controlled by epidermal growth factors and malignant mammary epithelial cell[8]. IL4 is a cytokine which is produced from TH2 cells. IL4 has a good response against parasitic and allergic reactions. This cytokines promotes the proliferation of tumour Associated Macrophages (TAM) towards M2 like phenotype and the expression of epithelial growth regulating factor receptor (EGFR) promotes the increasing chance of metastasis. Colony stimulating Factor (CSF1) also promotes the metastasis in the neoplastic cells [9]. IL4 and IL4a with the activation of intracellular regulating kinase ½, AKT, mTOR pathway promotes neoplastic metastasis towards distal organs [10]. IL4 activates the STAT 6. This STAT 6 affects the tumour prognosis and increases the chance of metastasis. So IL4-IL4a activity increases the chance of metastasis in the neoplastic cells.

IL6 is a pleiotropic cytokines which involved in the inflammatory response and haematopoiesis. IL6 promotes the signal transduction GP130. IL6 binds to JAK-STAT pathway, JAK1,JAK2, TYK2 and promotes the phosphorylation of GP130 that further allows the downstream signalling through STAT1 and STAT3, SHP2 and

PI3K pathways[11]. IL6 induce the CD8 T lymphocytes into cytotoxic lymphocytes and IL6 promotes the production of cRP, serum amyloid A, fibrinogen, hepcidin, and alpha1antichromotrypsin in the liver[12]. IL6 is a good prognostic marker to detect the metastasis properties in the neoplastic cell mostly in the breast cancer.

Table 1. The different types of interleukins and there expression on different types of cancer:

Name of Cancer	Name of Interleukin	Expression	Reference
Breast Cancer	IL1, 2,4,6,7,8,10,11,13,17,19,21,23,32,33	High	33
Lung Cancer	IL 1B, IL 17	High	34,35
Gastric Cancer	IL1,IL6,IL8,IL10	High	36
Prostate Cancer	IL1a, IL1B, IL6	High	37
Endometrial Cancer	IL6, IL11	High	38,39
HCC	IL18, IL6. IL33	High	40,41,42
Colon Cancer	IL22, IL6,IL4	High	43,44
Ovarian Cancer	IL6, IL11	High	45,46.
Cervical Cancer	IL6, IL2	High	. 47,48
GBM	IL1B,IL6,IL8	High	49

IL8 is another cytokines important in tumour metastasis and angiogenesis. Its receptors are CXCR1 and 2 and it is secreted fibroblast, stromal and endothelial cell [13,14]. IL8 is a chemoattractant of neutrophil, and IL8 alters the VEGF factor by which IL8 promotes metastatic property of neoplastic cells [15].IL10 is immunoregulatory cytokines which inhibits TH1, Cytotoxic T cell actives. IL10 diminishes the neoangiogenesis and reduce the MMP9 expression and thus reduce the chance of metastasis [16]. IL10 expression in a cell also signifies the less chance of cancer metastasis [17]. Thus IL 10 can be used to stop the cancer metastasis.IL17 are the proinflammatory cytokines which secreted from TH17 cells. IL 17A blocks SDF1 which promotes the metastasis thus IL17A axis always favours the metastasis [18].The IL19 is the cytokine which is mostly responsible for metastasis of lung carcinoma. It expressed in the advanced stage of the tumour increase the mitosis thus increase the chance of metastasis in a significant amount[19,20].The IL20 upregulates MMP9, MMP12, cathepsin K, Cathepsin G thus proliferation and migration of neoplastic cells happens and IL20 is mostly related to the metastasis breast cancer.

IL22 cytokines is related to breast cancer metastasis. It is secreted by TH1, TH17, TH22 and initiate lymphoid cells. IL22 overexpression shows very poor prognosis in case of breast cancer [21].

IL25 expression in breast cancer cell makes a poor prognosis although IL25 proliferation in the the lung CA makes a low prognosis [22]. One study shows that IL25 induced a phytochemical Q2-3 that can provide antitumorogenic activities [23].On the other IL30 is expressed in breast cancer and it triggers the proliferation, migration and inflammation of neoplastic cells [24].

5. Conclusion and future prospective:

According to our literature review it is again proved that IL has a great role in cancer metastasis and its developments other than body immune response. In this situation they can be acts as prognostic markers of some different cancer also. As researchers already started to use these molecules in therapeutics, more studies are warranted in this area to understand better its overall role and thus in future we can better treat cancer.

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9. Reference:

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