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Current Status of Interleukin-6 in Lung, Prostate, and Breast cancers

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Abstract : Interleukin 6 is a multifunctional cytokine which regulates different kind of functions in the immune system. Directly as well as indirectly it has a major in the cancer progression, particularly in leading cancers around the world. In Breast cancer it's showed a significant association in the serum level, but not to conclude the SNP. Among the prostate cancer patients, 174 G/C polymorphism and the GG+GC genotype play a major role in development. Lung cancer patients there were few studies done, in the serum level, also the polymorphism studied only from the western countries. We should go further with the emerging approaches in this Interleukins and their role in cancer biology.
Keywords: Serum level, Polymorphism, Growth factor, SNP.

Introduction

Interleukin 6

Like B-Cell differentiation factor, hybridoma growth factor, Interferon beta 2, BSF2, hepatocyte stimulatory factor, there are plenty of names for Interleukin 6 in biology, with the interferon beta 2 activity, when it was first identified as a B-Cell differentiation Factor[1]. but in continuous studies it didn't show the interferon beta activity. Every Interleukin belongs to one family, according to its structure and functionality, respectively IL-6 belongs to the Interleukin 6 family of cytokines, has some other members like leukimia inhibitory factor, oncostatin-M, ciliary inhibitory factor. [2]It's a different among other cytokines, having both pro and anti inflammatory functions, also called pleiotropic cytokine, which participates in the functions of hematopoiesis, inflammation, acute phase responses regulation, immune responses regulation[3].IL-6 has a range of cells for production; some are endothelial cells, monocytes, fibroblasts, macrophages. In particularly at the time of systemic inflammation, with the help of different stimuli responses, the macrophages produced IL-6[4].IgG,IgM,IgA plasma cell production and B cell differentiation, T cell proliferation promoted by IL-6.

In nature,184 amino acids in structure.Interleukin 6contain helix bunch composition, has 4 alpha helices as well as 2 components,which is IL-6Receptor and gp130,for the purpose of cell surface signalling.

There are two forms of IL-6R known respectively, soluble form and transmembrane form. but gp 130 will recruited when the IL-6 binds[2]IL-6R one of the member of cytokine receptor family, categorized by the N-terminial, which has 4 sealed cysteine residues[2]In the case of target cells,IL-6 binds to the receptor unit(low affinity receptor) which having 80-kd glycoprotein.

It's a multifunctional pleiotropic cytokine, which participates in the different functions. Since the discovery, still now it shows divergent functions in different disease, especially in autoimmune diseases and cardiovascular diseases. Because the level of IL-6 correlates with plenty of diseases, that's why people studied it's concentration and gene polymorphisms in IL-6.

IL-6 Signalling Pathways

Vast number of steps involved in the signalling pathway of IL-6. The IL-6 binding chain has two forms 55 kda soluble form and 80kda transmembrane form**.** Homodimerization will occur, when the IL-6 binds to either soluble or transmembrane form, at the same time gp130 will induce the downstream signalling pathways[5].IL-6,gp130 and IL-6R will form a hexameric structure in activated complex, because it's only receptor for IL-6, whereas the other family members like oncostatin M, IL-11, ciliary neurotrophic factor, leukemia inhibitory factor, cardiotrophin 1, IL-35 ,IL-27 will collectively share signal-transducing chain gp130[6].In activated gp130,will induce the downstream pathways, like mitogen-activated protein kinase (MAPK) pathway, (JAK)–STAT3 pathway[7].Further confirmation of receptor complex will confirmed by gp130 dimerization, continuously STAT pathway correlates with gp130 and work as a substrate for JAK/TYK. In this pathway. tyrosine phosphorylation presents in a single residue [8]. At the time of tyrosine phosphorylation, single serine residue will phosporylated in STAT3(Ser727) because of IL-6 response [9].Gene expression will induced by the nucleus,when the translocation and dimerization of STAT3 presents, and this lead to the some protein synthesis functions, exemplar, hepatocytes produce acute phase proteins[10].Having signal transducer and activator of transcription (STAT) and JAK pathway with tyrosine phophorylation, will mainly target interleukin responsible genes[11].

Signal transduction components like, SEK-1/MKK-4Rac-1, Vav, and MEKK having gp130 protein in IL-6-induced STAT3 phosphorylation and transactivation proved by a study[12].Many of the cytokine having this pathway, called GTP-binding protein Ras, include the signalling cascade of IL-6 and gp130 have the binding motif. Some intermediate steps like MAP kinase Kinase, MAPK and Raf, participates in this Ras pathway [6, 13-15].In further IL-6 nuclear factor activated by the MAP Kinase [16].High level expression of the NF-IL6 gene, induced by IL-6 binding activity, and activates theronine/serine protein kinases [17, 18].

Interleukin 6 and cancer

Role of this multifunctional cytokine is multifaceted, included paracrine and autocrine activities. Vast amount of IL-6 was produced by the different cancers like colon cancer, breast and prostate cancer, gp130 and gp80 subunits allowed these to respond IL-6.[19, 20].IL-6 has direct actions in osteoclasts, immune cells, endothelial cells, and osteoblasts[21].IL-6 has activating different downstream pathways, direct link in cancer progression and tumor cell proliferation. Some survival proteins expression increased by IL-6, like XIAP, Bcl-XL, Bcl-2, Mcl-1[22].High level of chemoresistence linked with high expression of these proteins[23].

Why Interleukin-6 as a marker in cancer

We have huge history approximately 150 years in the study of inflammation to cancer, from the first description by Rudolph, inflammation also significant risk factor in cancer development[24].But in inflammation, there were lot of cytokines participated but the Interleukin 6 took attention, due to its function in cancer development[25].Past studies proved that IL-6 has an important role in the cancer progression, also it levels associated with the development of some cancers[26, 27]since past years it was used in the cancer therapies[28]. In the results of different studies, example a study in chemotherapy results prediction, it predicted the efficiency of a drug called gemcitabine in pancreatic cancer [27].So that some research suggests it may be a biomarker for cancer prognosis.

Interleukin 6 levels and it's gene in Different Cancers

Prostate cancer

The largely common cancer among men, one of the largely leading death issues in US[29]. In past 20 years it was increased mortality than any other[30]. It commonly occurred as androgen dependent tumours, which used as a therapeutic technology for prostate cancer. In the case of androgen developed to prostate cancer, has various mechanisms to develop and initiate prostate cancer proliferation[31]. IL-6 has participating some pathophysiological processes in the prostate cancer, also some tumor types initated by IL-6, likely lymphoma, Kaposi's sarcoma, melanoma, ovarian carcinoma, renal cell carcinoma, and leukemia, prostate carcinoma and multiple myeloma[32]. Symptoms of morbidity in prostate cancer, has diffuse bone pain, anorexia, cachexia, anemia, asthenia, hypoalbuminemia, elevated acute phase proteins, with this symproms it will cause death without massive organ destruction[33].

In difference to growth factor activation of Androgen receptor, Mutated Androgen Receptor (LNCaP cells) proliferation was stopped by IL-6. So, these mechanism suggests that IL-6 will be a important factor in the androgen receptor activation as well as prostatic function maintenance [34]. From the past studies, we had learned that IL-6 has a role in prostate cancer development [33, 35, 36]. Adler et al. showed transforming growth factor-beta 1 along withIL-6 levels increased in patients than controls, also associated with cancer progression[35]. Drachenberg et al. suggested that IL6 might be a biomarker for prostate cancer [37].

In some times, especially at the time of cell death was induced by some chemotherapeutic agents, it protect the prostate cancer cells[38].In prostate cancer, concentrations of IL-6 as well as IL-6, IL-6R gene polymorphisms were did a crucial role in development. A study from 2001,IL-6 were increased in prostate cancer cells, prostatic epithelial cells secret the IL-6, in this case. Because in the LNCaP prostate cancer cells, normal prostatic epithelial cells,IL-6 was a growth factor, eightfold increased levels of IL-6R,elevated expression correlated with prostate cancer in *in vivo* study[39]. In polymorphisms associated with the prostate cancer several studies had done. Past study in 2001,174 G/C was associated with prostate cancer, will increase the risk. They found the strong relationship between in 174 G/C polymorphism and prostate cancer[40]. In a different method of both174G/C and 634C/G were analyzed in china, Hubai region among the Han peoples. But there were no significant relationship between 174 G/C, but the 634 G/C had some. In concisely GG+CG genotype had higher risk in the development of prostate cancer[41].

Few researchers try to conform this, so they did a literature search meta analysis, and stated there was no association in 174 G/C polymorphism in china as well as Asians, on the other hand they reported CC genotype might be a factor in African-American patients prostate cancer risk[42]. But last year 2015, there were vast number of studies in IL-6. The important polymorphism in the IL-6 gene,two polymorphisms 572C/G and 174G/C were analyzed in a huge population, 212 patients and 236 healthy individuals participated the study, they concluded IL-6 gene 572C/G polymorphism will affect the prostate cancer development[43] In contrast IL-6 inhibits the PDCD4 gene expression in the targeted modulation study[44]. From this everything we have an opinion in IL-6 gene polymorphisms and IL-6 concentration will play a important role in prostate cancer development.

Breast Cancer

The most common cancer among the worldwide women, with the manner of causation of a disease is multifactorial, also the development is extremely variable[45]. Long ago, the approach were started the impact of immune system, cytokines in the breast cancer [46]. Kozlowski et al.[47]Reported IL-6 levels were high in the breast cancer patients compared to the healthy women. They confirmed it associated with the disease progression and influence the disease in the clinical stage.one more study confirmed that high concentrations of the IL-6 patients died at the time of treatment [48]. There were vast number of studies[49-52] confirmed that IL-6 concentrations were associated to the development of the breast cancer patients in the clinical stage.

After this confirmed studies the scenario changed, instead of looking concentrations of IL-6, researchers tried the IL-6 gene polymorphisms, in breast cancer patients.In 2009, based on the former studies in IL-6 gene polymorphisms, Cherl et.al, [53] conduct astudy; found four novel polymorphic regions in the breast cancer patients. They actually tried to prove the 174 G/C polymorphism in IL-6, whether associated with the breast cancer patients. But they didn't found any association, in this region.Based on the previous studies a metadata analysis was done.[54]. Finally they came a conclusion it's very difficult to identify, a particular SNP associated with breast cancer risk, also stated there was no correlation between 174G/C polymorphism in IL-6 and breast cancer development. Continuous studies also didn't prove the relationship in this region[55]. So the study in IL-6 and breast cancer had changed, in past years. Whether the paracrine or any other effects in IL-6, will helps for the cancer cell proliferation, based on these questions, a study was performed, an optical labelling assay, and it showed it had a paracrine effect in this disease, also help for the proliferation of the other cancer cells[56],along with this targeting the signal in this pathway will helpful to prevent the disease development[57]. In the path of breast cancer treatment, now the trend entirely changed, because to identify the single nucleotide polymorphism, which will contribute to the disease progression is very difficult. So target the signalling pathways and stop the concentration of IL-6 might be helpful, also helpful for find a new diagnostic method.

Lung Cancer

Leading cancer in the world,due to pollution along with some environmental factors. One of the cancers leading to the death immediately, with approximately 11 million new patients treated with every year. Almost 1 in 8 might be a lung cancer patient. In the case of lung cancer, has two types, non-small cell lung cancer and small cell lung cancer. Variety of environmental factors contributed to the disease, but smoking is the major factor in disease development.[58-62]. In 1995, first study conducted in the IL-6 serum level, didn't show any significant association[63].afterward a huge number of patients undergone the serum level measurement, proved that high level of IL-6 correlated with lung cancer[64]between these two studies there were vast work done in the IL-6 gene polymorphisms. A meta analysis from Zhou et.al., 2012 [65] revealed more research need to conclude the IL-6 level in the lung cancer development. Some researchers studied only the 174 G/C polymorphism in the different populations around Europe. But these studies failed to prove the association of IL-6 174 G/C polymorphism and lung cancer risk. [66-70].In contrast, Some studies try to prove IL-6 gene 634C/G polymorphism might be the risk factor, in this also failed, because of there were no associations between this. In a same, there were two different Meta analysis performed and both got opposite results. At the month of January[71]the Meta analysis suggests IL-6 gene 634C/G polymorphism might be the risk factor, with the help of past 10 relevant studies. On the other hand, next month results showed there were no association in IL-6 gene 634 G/C polymorphism in lung cancer patients[72].

In the case of lung cancer it's difficult to conclude a result with this few works. Further we need to change our approach of the study and must find a clear target, to cure this vulnerable disease.

Conclusion

We need to study more, with high number of patients, to conclude whether this serum levels of IL-6 and it's gene polymorphism associated to cancer or not. Because past studies showed that correlation between this will increase risk, but another research showed it can't. We are in the era of genome wide association studies, so need to evaluate this genes functionality in the cancer development, and try to diagnose the disease instead of repeating same type of approaches.

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