Cancer is a Genetic or Immunological or Genetically Mediated Immunological Disorder or Immunologically Mediated Genetic Disorder

Shrihari T.G

Introduction

Cancer is a major threat to mankind. Majority of cancer more than 90% of all cancers are due to external environmental factors such as tobacco, alcohol, infectious agents (HPV, EBV), dietary factors,chemical ingestion (Benzele, silica, carbon monoxide, arsenic) leads to various types of cancers such as oral camcer, leukemia,lung cancer, gastric cancer, Breast cancer, colo rectal cancer, lymphomas, oropharyngeal cancer, oesophageal cancer.25% of all cancers due to chronic inflammation or infection.Chronic inflammation is considered as a seventh hallmark of cancer. Chronic inflammatory mrdiators such as cytokines, chemokines, growth factors, proteolytic enzymes are released from inflammatory cells such as neutrophils, macrophages, mast cells, dendritic cells,natural killer cells, T and B lymphocytes. IL-1β, TNF-α, COX-2 inflammatory mediators activate NF-KB a key transcription factor, TNF-α activate AP-1 transcription factor, EGF, FGF, IL-6, IL-10, PDGF activate STAT3 transcription factor.

Keywords: NF- KB, S TAT-3,IL-1,IL-6,P53.

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I. INTRODUCTION

Cancer is a major threat to mankind.Majority of cancer more than 90% of all cancers are due to external environmental factors such as tobacco,alcohol,infectious agents (HPV, EBV) ,dietary factors,chemical ingestion (Benzele, silica, carbon monoxide, arsenic) leads to various types of cancers such as oral camcer, leukemia,lung cancer,gastric cancer, Breast cancer, colo rectal cancer, lymphomas, oropharyngeal cancer, oesophageal cancer.25% of all cancers due to chronic inflammation or infection.Chronic inflammation is considered as a seventh hallmark of cancer.Chronic inflammatory mrdiators such as cytokines, chemokines,growth factors, proteolytic enzymes are released from inflammatory cells such as neutrophils, macrophages, mast cells, dendritic cells,natural killer cells, T and B lymphocytes. IL-1β, TNF-α, COX-2 inflammatory mediators activate NF-KB a key transcription factor, TNF-α activate AP-1 transcription factor, EGF, FGF, IL-6, IL-10, PDGF activate STAT3 transcription factor. Both NF-KB and STAT-3 transcription factors work together involved in cell proliferation by activation of cell cycle regulatory proteins such as cyclin D,E, cell survival by activation of BCL-2, BCL-XL anti apoptotic proteins,angiogenesis by IL-8, COX-2, VEGF, immune modulation by IL-10, TGF-β, iNOS, IDO, genomic instability by (ROS,RNS, AID, NO)invasion and metastasis by UPA (uro kinase plasminogen activator),MMP'S-2,9 involved in tumor progression(1-7).

HIF-1α transcription factor for IL-8,COX-2,VEGF inflammatory mediators activated in hypoxic tumor micro environment involved in angiogenesis and immun-omodulation. NF-KB a key transcription factor involved in tumor progression in inflammatory tumor micro environment by expression of inflammatory mediators antagonise P53 tumor suppressor gene,a guardian of the genome mutated in more than 50% of all cancers by nitric oxide (NO),ROS,RNS free radicals,AID(activation induced cytidine deaminase)enzyme. NF-KB a key transcription factor involved in conversion of TH1 cymphocytic type to TH2 lymphocytic type mediated by IL-4,STAT-6 transcription factor release IL-4, IL-5,IL-13 pro-inflammatory cytokines along with TH17 cells involved in immunemodulation. Altered induced Tregs (i T regulatory cells) formed from TH1 cells mediated by TGF-β release IL-2, IL-3, IL-4, IL-5,IL-10,IL-17 pro-inflammatory cytokines involved in chronic inflammation, tissue damage, and immunemodulation. Chemotactic cytokines are chemokines, which are involved in recruitment of immune cells to the inflammatory site. Chemokines are involved in tumor progression by expression of it's receptors on leucocytes produced by tumor and stromal cells. Chemokines involved in recruitment of neutrophils are CXCL1, CXCL2, CXCL3, CXCL5, CXCL6, CXCL7,CXCL8, chemokines involved in recruitment of dendritic cells, macrophages, natural killer cells by CCL2, CXCL12-CXCR4, CCL4,CCL5,MCP-1. Chemokines involved in recruitment of lymphocytes and natural killer

cells by CXCL12- CXCR4, CXCL9, CXCL10, CXCL11,CCr7-CCL21,CXCL19,CCL21(1-5,6,7,8).

Activation of tumor promoter genes such as C-MYC in lung cancer and neuroblastoma, RAS oncogenes in lung cancer,colon cancer, pancrease,cervical cancer, bladder and kidney cancer, RET oncogene in papillary thyroid cancer, PDGF in brain tumor, abl in acute lymphoblastic leukemia and chronic myeloid leukemia, ERB-B1 in breast cancer and squamous cell carcinoma of lung, ERB-B2 oncogene in breast and ovarian cancer. Suppression of tumor suppressor genes such as VHL/HIF in small cell lung cancer ,TGF-β in breast cancer, PTEN in lymphoma, endometrial carcinoma,hepatocellular carcinoma, colon cancer, P53 tumor suppressor gene in head and neck cancer,oro-pharyngeal cancer, RB gene in retinoblastoma and osteosarcoma, APC/β-catenin in gastric carcinoma, colon cancer, and pancreatic cancer, BRCA1 and BRCA-2 in breast and ovarian cancer, NF-1 in neuroblastoma, neurofibromatosis type1, sarcomas in various types of cancers induced transcription of chemokines such as CXCL4 and induced production of CXCL5 and CXCL12 chemokines facilitates recruitment of MDSC(myeloid derived suppressor cells) involved in metastasis, CXCL8 chemokine involved in angiogenesis, recruitment of monocytes and dendritic cells by CCL2,CCL20, CXCR4 promotes metastasis. Activation of inflammatory mediators such as IL-1β,TNF-α, COX-2, and IL-6 involved in activation of NF-KB a key transcription factor and STAt-3 transcription factors. IL-1β,TNF-α, and COX-2 inflammatory mediators activate NF-KB a key transcription factor, IL-6, IL-10, EGF,FGF,PDGF activate STAT-3 transcription factor, Both NF-KB and STAT-3 transcription factors work together induce inflammatory mediators involved in cell proliferation by activation of cyclin D,E cell cycle regulatory proteins, cell survival by activation of BCL-2,BCL-XL anti-apoptotic proteins, angiogenesis by IL-8,COX-2,VEGF , genomic instability by ROS,RNS,iNOS,AID (Activation induced cytidine deaminase) enzyme, immunemodulation by IL-10, TGF-β, IL-4, IL-5, IL-13,Tregs, chronic inflammation by IL-1β,TNF-α,and IL-6, invasion and metastasis by UPA (Urokinase plasminogen activator), MMP's 2,9 (Matrix mettallo proteinases 2,9) , all these changes involved in tumor progression (8-11,12,13). Cancer is a complex interaction between cancer cells, immune cells, stroma, and genes. Thorough understanding of interaction between these helps in understanding of cancer pathogenesis and therapeutic applications.

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