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RESEARCH ARTICLE

ROLE OF INTRA TUMOR BACTERIA IN GENESIS OF CANCER DRUG RESISTANCE- A REVIEW

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ABSTRACT

Genesis of cancer is a multifactorial. It has been found to be associated with genetic factors and oncogenic viruses and oncogenic bacteria. Recent studies found the presence of intra tumor bacteria. These have been associated with the metastasis and anti-cancer drug resistance. In the present review we update the role of intra tumor bacteria in the development of anti-cancer drug resistance.

INTRODUCTION

Cancer has been associated with high morbidity and mortality. It is estimated that the nearly 19.3 million cases of cancer occur every year and common cancer include lung cancer, breast cancer, bowel and prostate cancers with the mortality of 10.0 million worldwide [1]. Several factors are known to be involved in the cancer genesis including genetic factors, exposure to toxic chemical agents, ionizing radiations, oncogenic viruses, oncogenic bacteria and parasites. Several cancer treatment modalities are involved including surgery, radiation therapy, chemotherapy, hormone therapy, and bone marrow transplant. Chemotherapy acts as a saviour in several cases, but studies have shown the failure of chemotherapy due to metastatic nature of the cancer as well as development of anti-cancerdrug resistance.[2] Resistance to therapy is multifaceted. The mechanism of drug resistance was both intrinsic and extrinsic in nature including presence of tumor heterogeneity, tumor microenvironment, and presence of cancer stem cells and inactivation of anticancer drugs. Different mechanisms have been evolved in the genesis of cancer drug resistance including the increase in the drug expulsion from the cells, reducing the intake of the drug into the tumorcells.The inhibition of the cell death due to upregulation of anti-apoptotic nature in tumour cells has also been known to be involved in the development of drug resistance. Several other factors such as changing the drug metabolism, alteration in the drug targets, gene amplification and epigenetic alterations are known to in multi drug cancer resistance. [2]. Bacteria play an important role in the genesis of cancer as well as in chemotherapy. The chronic infections caused by *Helicobacter pylori* promote the development of the gastric carcinoma through the epithelial injury and inflammation. [3]. Therapeutic bacteria were found to be one of the agents contributing to the treatment and also aid in overcoming the limitations in the conventional cancer therapy. Genetically engineered bacteria can aid in the treatment targeting the hypoxic regions of the tumor, penetrate the tissues leading to the release of different enzymes favouring the death of cancer cells. [4] Recent studies found that presence of intra tumor bacteria has been noted previously presumed as sterile. The cancer tissue might have acquired bacteria through several means including the direct invasion through mucosal barrier, spread from the adjacent tissue or haematogenous spread. [5] Intra tumor bacteria were heterogeneous in nature. Firmictures and Bacteroides were predominantly found the colorectal carcinoma. Pancreatic cancer was found to be associated with Proteobacteria and Actinobacterial families, which are also highly prevalent in gastrointestinal carcinoma.[5] These intra tumor bacteria found to be associated with the

cancer development, its progression, metastasis and development of anti-cancer drug resistance. A study from Geller et al found that bacteria has the ability to metabolize the chemotherapeutic gemcitabine (2',2'-difluorodeoxycytidine) into its inactive form, 2',2'-difluorodeoxyuridine. The inactivation of the drug is due to the production of cytidine deaminase (CDD_L), which has ability to convert active gemcitabine into inactive form. The cytidine deaminase enzyme is mainly produced by intra tumor bacteria Gammaproteobacteria. [6]. Study conducted in colon cancer mouse model found that gemcitabine resistance was induced by intratumor Gammaproteobacteria, dependent on bacterial CDD_L expression, and was abrogated by co-treatment with the antibiotic ciprofloxacin. A study from Thomas et al has found that intratumor bacteria promote the gemcitabine resistance in pancreatic adenocarcinoma. [7] Xi and coworkers established through application of nanoenzymes, which have an ability to bind to the active centre of CDD and preventing its action to convert the active gemcitabine to inactive form. In mouse cancer model with the intratumor bacteria, Xi et al has successfully reversed the gemcitabine resistance and restored the tumorsusceptibility to gemcitabine.[8].

CONCLUSION

We conclude that presence of intra-tumor bacteria evolved the cancer cells ability to develop drug resistance. The presence bacterial heterogeneity, production of different enzymes have an ability to inactivate the anti tumor drugs. Further studies should focus on the research to evaluate different mechanisms of intratumor bacteria promoting drug resistance in cancer and counter actions to prevent the spread of cancer as well as drug resistance.

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