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EGFR mediated arsenic induced carcinogenesis: An overview

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Abstract
EGFR is a receptor tyrosine kinase (RTK) localized on the cell face (Fig. 1). As one of the erbb family receptors (EGFR, erbb2, erbb3, and erbb4), EGFR is actuated by specific ligands, and there are 7 endogenous EGFR ligands (epidermal growth factor (EGF), transubstantiating growth factor-α (tgfα), HB-EGF, amphiregulin (AREG), betacellulin (BTC), epigen (EPGN), epiregulin (EREG)). Arsenic is a potent poison, due to its lack of color, taste and odor. Also, the symptoms from arsenic poisoning are very similar to the symptoms of food poisoning, thus rendering it nearly untraceable without sophisticated analytical procedures. Proposed mechanisms of arsenic- convinced carcinogenesis include oxidative stress, epigenetic changes including histone revision, mirna expression, and DNA methylation, aneuploidy, and activation of oncogenic pathways, similar as the epidermal growth factor receptor (EGFR). The overexpression of EGFR and its association with a poor prognostic can be explained by increased spots for the ligands to bind to the receptors, leading to enhanced downstream signaling events, similar as proliferation. An increase in conflation of ligands above the rudimentary situations also triggers improvement of the EGFR-convinced activation of proliferative pathways. High situations of EGFR ligands, including EGF, tgfα, AREG, and BTC, were observed in cancers.

Keywords: Arsenic, EGFR, Carcinogenicity, Leukemia, Mutations

Introduction
Arsenic is a potent poison, due to its lack of color, taste and odor. Also, the symptoms from arsenic poisoning are very similar to the symptoms of food poisoning, thus rendering it nearly untraceable without sophisticated analytical procedures [1]. Arsenic was classified as group I "carcinogenic to humans" by the International Agency for Research on Cancer (IARC) based on epidemiological carcinogenicity evidence in human and in animal models [2]. Arsenic is ubiquitous in the environment, and it has been used by of human civilization since ancient times, both for constructive and destructive purposes [3]. The epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase confined on the cell surface. Overexpression of EGFR has been used as biomarkers for many altered forms of cancers, counting lung cancer. There is a strong association between arsenic and lung cancer development, although the mechanism is unclear [1].

Arsenic uses in medical applications
In the 18th century, Thomas Fowler, an English physician, produced Fowler's Solution, a potassium bicarbonate-based arsenic solution, which was widely used to treat many conditions such as asthma, convulsions [3] and psoriasis [4]. Also recognized as a cancer of the blood cells, leukemia is related with abnormally high number of white blood cells. Arsenic was also used to treat leukemia; with the Fowler's Solution, the number of white blood cells declined dramatically in leukemia patients over 10-weeks carcinogen and is prominently associated with skin, lung, and bladder cancers. Arsenic hinders repair processes of UV-induced photo adducts and its role in repressing DNA repair processes also contributes to chemotherapeutic effect [5]. Wang *et al*. Showed combination treatment of arsenic with cisplatin is more effective in treating hepatocellular carcinoma than cisplatin treatment alone [6].

Health effects of acute and chronic arsenic exposure
Arsenic toxin is largely dependent on its cure and duration of exposure time, as its acute toxicity is different from habitual toxicity. Generally acute toxin results from accidental ingestion of high situations of arsenic. Ingestion of large quantities of arsenic will bear treatment, similar as decontamination, administration of intravenous fluids, and chelation remedy. The symptoms, including diarrhea, puking, dehydration, and hypotension, are generally observed in workers who ingest high

situations of arsenic in their workplaces from dust and smothers. In severe cases, the symptoms can lead to death, primarily due to dehumidification and shock [7]. The skin, lungs, and liver are the main target spots, as arsenite, especially, readily interacts with thiol or sulfhydryl groups in towel proteins of the organs [21]. The response between arsenic and thiol groups can hamper critical biochemical events that lead to major venom, and symptoms include skin lesions, pulmonary complaint, hypertension, cardiovascular complaint, diabetes, neurological diseases, cancer, and death [8-9].

Table1: Acute and chronic arsenic toxicological effects on human health

Acute Arsenic Exposure (<24 hours)	Chronic Arsenic Exposure (>3 Months)
Vomiting, diarrhea, dehydration, Hypotension, abdominal pain, renal failure.	Cancer in many organs, skin pigment Changes, cardiovascular disease, Respiratory disease, diabetes, Hypertension, skin lesions, neurological disorders

Arsenic and lung cancer

A common type of cancer in the U.S. that's convinced by habitual exposure of arsenic is lung cancer. The two major forms of lung cancer are non-small cell lung melanoma (NSCLC), and small cell lung melanoma (SCLC). NSCLC accounts for further than 80 of all lung cancer. NSCLC can be divided into three major histological subtypes scaled- cell melanoma, adenocarcinoma, and large- cell lung cancer. Adenocarcinoma is the most common type of lung cancer in cases who have no way smoked. Scaled- cell melanoma is also constantly observed in non-smokers, and is largely associated with habitual enic-induced carcinogenesis.

Proposed mechanisms of arsenic- convinced carcinogenesis include oxidative stress, epigenetic changes including histone revision, miRNA expression, and DNA methylation, aneuploidy, and activation of oncogenic pathways, similar as the epidermal growth factor receptor (EGFR). The EGFR is a well- established biomarker of cancer, and studies have planted the EGFR is overexpressed in a variety of excrescences and cancer cells, which correlates with poor case prognostic, including NSCLC [12]. Both former studies and our primary data have shown acute arsenic exposure induces overexpression of EGFR in mortal bronchial epithelial cells [13]. Despite a direct association between supraphysiological situations of arsenic and lung cancer, how habitual exposure to “a physiologically applicable” position of arsenic affect EGFR expression and signaling aren't known.

EGFR

EGFR is a receptor tyrosine kinase (RTK) localized on the cell face (Fig. 1). As one of the erbb family receptors (EGFR, erbb2, erbb3, and erbb4), EGFR is actuated by specific ligands, and there are 7 endogenous EGFR ligands (epidermal growth factor (EGF), transubstantiating growth factor-α (tgfα), HB-EGF, amphiregulin (AREG), betacellulin (BTC), epigen (EPGN), epiregulin (EREG)). Of these ligands, HBEGF and BTC are known to have high affinity for the receptor and have fairly high downstream goods [14]. The EGFR is a critical element in development. The EGFR expression was observed in embryogenesis, and its ligands, specifically EGF and tgfα, were also expressed from 4-to 8- cell stage of embryogenesis [15]. When the receptor isn't enthralled by a ligand, the cysteine rich regions of the extracellular sphere of the receptor interact with each other and maintain an “unrestricted” conformation. When a ligand binds to the ligand binding disciplines of the extracellular sphere, the EGFR undergoes a conformational change, exposing cysteine-rich regions. These regions, also, interact with other exposed cysteine-rich regions of another erbb family receptor. This allows receptor dimerization and activation of the natural kinase exertion. Once actuated, the intracellular kinase from one receptor Trans-phosphorylates tyrosine remainders on its receptor brace. These recently formed phosphotyrosines also serve as docking spots for downstream signaling proteins that intervene cell proliferation, survival, tumorigenesis, and isolation.

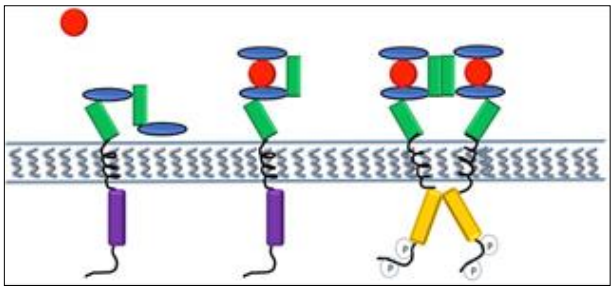

Fig 1: Red=ligand; green=cysteine-rich regions; blue=ligand-binding domains; purple=inactive kinase domains; yellow=active kinase domains

EGFR and Cancer

There are four main events that can undo the EGFR nonsupervisory mechanisms, which all contribute to cancer development 1) overexpression of EGFR, 2) overproduction of its ligands, 3) indecorous receptor trafficking, and 4) the EGFR kinase sphere mutations. Under pathological conditions, similar as cancer, the normal nonsupervisory mechanisms of the signaling pathways are perturbed, performing in hyper activation of the signaling pathways. The overexpression of EGFR and its association with a poor prognostic can be explained by increased spots for the ligands to bind to the receptors, leading to enhanced downstream signaling events, similar as proliferation. An increase in conflation of ligands above the rudimentary situations also triggers improvement of the EGFR-convinced activation of proliferative pathways. High situations of EGFR ligands, including EGF, tgfα, AREG, and BTC, were observed in cancers [16]. Dislocation of proper EGFR trafficking is known to contribute to cancer development substantially due to poor down regulation of the receptors and sustained downstream proliferative signaling. Not only overexpression of the wild type EGFR, but also expression of the mutant EGFR kinase sphere can contribute to cancer development. The most common EGFR kinase sphere mutation is egfrviii, which is an omission of remainders from 6 to 273 [17].

EGFR-targeted chemotherapy

Because of the significance of EGFR in cancer development, there have been several chemotherapeutic agents that target EGFR. The EGFR-targeting chemotherapeutic agents can be divided into two main classes’ monoclonal antibodies and small patch kinase asset.

An illustration of the monoclonal antibody is Cetuximab, which targets the extracellular sphere of the receptor to help ligand receptor relations. This medicine is approved for treatment of cancers, similar as colorectal cancer and scaled cell melanoma of the head and neck (NCI, 2018). Erlotinib and gefitinib are exemplifications of TKI, which bind to the kinase sphere of the receptor to help activation of the downstream proteins and their signaling [18].

GFFR and arsenic-induced carcinogenesis

Arsenic readily accumulates in epithelial cells as they've high content of thiol groups, and EGFR plays a critical part in epithelial development. The commerce between arsenic and thiol groups supports arsenic part in lung cancer development through EGFR signaling axis in epithelial cells. In this thesis, we suggest a implicit part of habitual arsenite exposure in the regulation of factors of the EGFR signaling axis. A former study used micromolar range of arsenite, and observed increased position of EGFR ligand, specifically HB-EGF [19]. HB-EGF is seen in a variety of cancers, similar as colorectal, cervical, bone and gastric cancers [20]. There's a spare quantum of studies that observed the effect on the receptor the EGFR endocytic trafficking pathway is a implicit target point of habitual arsenic to induce overexpression of EGFR in the cells. Dislocation of proper EGFR trafficking is known to contribute to cancer development, similar as lung, pancreatic, and bone cancers [21]. A study has shown arsenic increases protein situations of Rab4, a protein involved in the recycling of EGFR [22]. This study suggests an implicit part of arsenic in altering the endocytic trafficking of EGFR. Under normal conditions, EGFR internalizes via clathrin- intermediated endocytosis, but at high boluses of EGF, the EGFR undergoes clathrin-independent endocytosis, including caveolin intermediated endocytosis [23]. The EGFR endocytic trafficking pathway is a implicit target point of habitual arsenic to induce overexpression of EGFR in the cells. Dislocation of proper EGFR trafficking is known to contribute to cancer development, similar as lung, pancreatic, and bone cancers [24]. Despite of the significance of proper EGFR trafficking in cancer development, there has been no study that tested differences in the route of EGFR trafficking from habitual arsenic exposure.

Conclusion

This review suggests that arsenic is a powerful poison that causes many types of cancers including lung cancer. Arsenic causes overexpression of EGFR, which is a tyrosine kinase receptor. Proposed mechanisms of arsenic- convinced carcinogenesis include oxidative stress, epigenetic changes including histone revision, mirna expression, and DNA methylation, aneuploidy, and activation of oncogenic pathways, similar as the epidermal growth factor receptor (EGFR). In severe toxicity, the symptoms can lead to death, primarily due to dehumidification and shock.

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