

Epigenetic changes and their reversal using natural compounds

[Science](#), [Genetics](#)



Cancer is known to be a multi-step process that involves different stages like initiation, promotion, progression and metastasis. Chemical carcinogens including Arsenic, Chromium, Lead, Mercury, Chloroform, PAH (Poly aromatic hydrocarbon, THM (Trihalomethanes) elements can change any of these processes to induce their carcinogenic effects. Approximately 2% to 8% of all cancers are thought to be due to carcinogens present in environment. In addition to this, environmental cancers have their own characteristics, e. g., specific chemicals and their associated cancers, multiple factors, multiple causes and interaction, or latency period.

Epigenetics is the study of heritable changes in gene expression that occur without causing any change in DNA sequence. Epigenetic mechanisms are flexible genomic parameters that can alter genome function, but also provide a mechanism that allows for the stable DNA propagation from one generation of cells to the next. Hypermethylation is a covalent modification, heritable by somatic cells after cell division. 5-methyl-cytosine (5MeC) represents 2-5% of all cytosines in mammalian genomes and is found primarily on CpG dinucleotides. Modifications of DNA and histones are also reversible making them good targets for therapeutic interventions.

Epidemiological studies show that exposure to these contaminants leads to gene specific DNA hypermethylation in some genes like p53, DAPK, p16, APC etc.

Since these epigenetic modifications are reversible, the goal of epigenetic therapy is to reverse the abnormal alternations that occurred in cancer cells and induce tumor suppressor genes reactivation, leading to cancer cell

differentiation and cell death. Thus, epigenetic enzymes will be the attractive drug targets in the field of drug discovery. Many anti-cancer drugs are derived from natural compounds and there have been reports of natural compounds modulating epigenetic activity for different types of Cancers. These include Curcumin, Resverstrol, Genistein, Menthol, indole-3 carbinol, and omega-3 fatty acids etc. Accumulating evidence clearly show toxic metal exposure which leads to alteration and induction of epigenetic marks in epidemiological and experimental studies. Changes in Epigenetic marks at a global level require further evaluation for their involvement in epigenetic process.

Introduction

Nearly 80% of India's rural drinking water comes from underground sources with contamination plaguing towns like Gorakhpur, Uttar Pradesh. According to a 2012 study Arsenic contamination has been widely reported across northern Indian states like Punjab, Haryana, Himachal Pradesh and Uttar Pradesh. Groundwater arsenic contamination has also been found in the lower Ganga plain of West Bengal, Bangladesh and the Terai region of Nepal. Arsenic and fluoride are commonly found in groundwater where chemicals have leached from the bedrock due to overexploitation of the source.

Fluoride, arsenic and iron are known to have caused encephalitis, jaundice and typhoid, mostly among the poor who live in dismal sanitation conditions.

Heavy metals are likely to rush in from industrial waste dumped untreated into water-systems while nitrates may be distributed on to the surface due to excessive and prolonged use of fertilizers.

Most of the water contamination is triggered by anthropogenic factors like industrial effluents leaching into the ground. Groundwater pollution is tough but once polluted; it can be extremely difficult to get rid of. It has been identified that in urban areas like Greater Noida, heavy metals like lead and chromium also permeate into groundwater. The prolonged unchecked industrialization, and urbanization has polluted the two major water bodies – the Hindon and Yamuna rivers that flow through the crowded floodplains in Uttar Pradesh. In Yamuna Floodplain Project it was studied that millions of tonnes of sewage from Delhi and Ghaziabad causing contamination in these two primary water bodies.

Overexploitation of groundwater resources due to population explosion is also making the problem more tedious in many regions of India as well as in other countries.. The National Capital Region Planning Board estimates that seven of nine districts in Delhi are categorized as overexploited with respect to dynamic groundwater resources.

Pollutants and their Carcinogenicity

High content of heavy metals in water and sediments in river Ganges downstream has been reported (Singh et al., 2005). Arsenic is not contained so much in the Earth's crust but greatly concentrated in pyrite, hydrous Fe oxides and sulfur compounds (Smedley and Kinniburgh 2002). It is known that As would be easily solubilized in water from these minerals depending on pH, redox conditions and temperature (Smedley and Kinniburgh, 2002). Nickson et al. (1998) suggested that As may be released from As-rich Fe oxyhydroxides into groundwater under reductive conditions in alluvial

sediments in Bangladesh and West Bengal. Increased usage of groundwater for drinking in these areas has caused serious health problems (Bagla and Kaiser, 1996; Nickson et al., 1998), because inorganic As is carcinogenic and causes skin and various internal cancers (IARC, 1980; WHO, 2001). Arsenic distribution is also affected by anthropogenic activities, such as mining and smelting operations, coal-fired combustion, and use of agricultural herbicides, pesticides, and medicinal and cosmetic products. (Orloff et al., 2009), but the major source of As, in general, is chemical weathering of rocks (Bhattacharya et al., 2007). A recent survey from rural Gangetic basin, North India, cluster analysis revealed a positive correlation of nickel, cadmium and chromium in water with high prevalence of gallbladder diseases in adjacent villages in Vaishali district, Bihar (Unisa et al., 2011). Cr⁶⁺ was detected in about one-third of 7000 drinking water sources surveyed by the State of California. Cr⁶⁺ contamination of groundwater can be due to natural conditions or to discharges from industrial activity such as chromium ore processing, metal plating, and use of Cr⁶⁺ as an anticorrosion agent in cooling water (Ball et al., 2004 Fryzek et al., 2001). A study published in 1987 found elevated mortality rates for total cancer, stomach cancer, and lung cancer in communities with Cr⁶⁺ contaminated water in Liaoning Province, China (Zhang et al., 1987). Chronic ingestion of As-contaminated drinking water produces lesions to the skin, skin cancer, and various other types of cancer (lung, kidney, liver, and bladder). Because inorganic As has a half-life in the body for few days (it has been reported that 45–85% of arsenic ingested in the human body is excreted in urine within 1–3 days), its presence in the urine has been used as biomarker of

recent exposure (Crecelius, 1977; Hwang et al., 1997; Calderon et al., 1999; Karagas et al., 2001; Chen et al., 2002). The heavy metals Cd, Ni, Pb and U are known to have a number of negative impacts on human health, such as DNA damage, cancer and damage of the central nervous system (Stohs and Bagchi, 1995). Lead is a “ possible human carcinogen” because of inconclusive evidence of human and sufficient evidence of animal carcinogenicity (WHO, 1996). Nickel is a “ probable human carcinogen” (International Committee on Nickel Carcinogenesis in Man).

Lead is a contaminant in food and water. Total diet studies in industrial countries indicate a daily

Intake of lead of the order of 200-300, microgram. Intake from drinking water provides about 20 microgram and inhalation of city air about another 20 microgram per day. The unregulated discharge of industrial wastes is also seen to pose significant risks to the food system (Marshall et al., 2017). Not all villages have abandoned agricultural practices, but the scarcity of freshwater has led many farmers towards the irrigation of food crops such as cereals and vegetables with wastewater that can contain industrial pollutants (Marshall et al., 2005). The main contaminants identified within the effluents of these industries include high levels of organic pollutants as well as high concentrations of heavy metals. Human risk was assessed in people exposed to trace metals using exposure risk assessment model indicated Arsenic was the most important pollutant causing noncarcinogenic and carcinogenic concerns, particularly for sensitive children. As, Sb and Se were the largest contributors to chronic risks while Ni, Al, Fe and Ba were the least contributors in both the dry and rainy seasons (Zhang et al., 2010) The

levels of these contaminants in the river and groundwater are consistently above permissible limits and as a result the water is considered unfit for recreational activity and the sustenance of aquatic organisms (Rizvi et al., 2015). High values of heavy metals are frequently documented in the peri-urban (Singh et al., 2010) and can be extremely toxic to aquatic organisms as well as to humans, where long-term ingestion of water polluted with heavy metals can be devastating, leading to the development of a number of cancers, neurological disorders, and even death. In Arthala colony, lead has been found in the groundwater in concentrations more than three times the permissible limits of the WHO (Lewis, 2000).

Synthetic chemicals disperse into lakes and streams from atmospheric fallout, example Natural seepage problems of oil and polycyclic aromatic hydrocarbons (PAH) into the continental shelf and beaches pose a health problem. Wilson et al., 1974 coworkers estimate the release of carcinogenic PAH into the marine environment to occur at the rate of 0.2×10^6 to 6×10^6 metric tons per Year. THM are widely found at concentrations ranging from less than one part to several hundred parts per billion, usually at much higher levels than other halogenated hydrocarbon contaminants (Symons, 1975). Disinfection by chlorination has been used in most large U. S. cities with surface water supplies since the early 20th century (Wolman et al., 1919). Formation and escalation of levels of the suspected carcinogen, chloroform, from a few micrograms per liter concentration in raw water to several hundred micrograms per liter in drinking water, an enhancement attributed to the effect of chlorination. on humic acids The geographical

correlation studies appeared to show a stronger association than chloroform with certain cancer mortality rates, especially bladder cancer. The brominated alkanes have not been extensively bioassayed in experimental animals for carcinogenic activity. (Cantor et al., 1976).

Dichloro diphenyl Trichloroethane (DDT) was the first synthetic insecticide used in our country (Joshi, 2005).