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Research Article
Molecular Mechanism of Formaldehyde and Protein Interaction in Human Cancer Cell

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Abstract

Background: Formaldehyde ($H_2C=O$) is a flammable, colourless reactive compound and readily polymerized gas at normal pressure and room temperature with a relative molecular mass of 30.03 and a pungent odour. **Methodology:** Formaldehyde in aqueous solution enters the bloodstream directly. These events are most likely occur in dialysis or in surgery with assisted circulation, which is the dialysis machine and tubes are disinfected with formaldehyde. **Results:** It is observed that proteins (DHRS4, AOC3, ALDH3A1, ADH5, FOS, TRPA1, DMGDH, SARDH, PIPOX and SHMT2) that interacted with formaldehyde compound out of which the fructooligosaccharide (FOS) is protein that work in cancer case. The STITCH method was used to analyse interaction between formaldehyde and protein, STRING for analyse protein interaction and KEGG pathway to generate the pathway of molecular mechanism in cell. **Conclusion:** The FOS have role in response to calcium ion, if the formaldehyde bind with fructooligosaccharide, it will be doubt the homeostasis of altered Ca^{2+}, cation and ion channel activity.

Key words: Cancer, formaldehyde, protein interaction, STRING program, KEGG pathway

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Formaldehyde is compound that have common synonyms name like methanal, methylene oxide, oxymethylene, methylaldehyde, oxomethane and it consist of C, O and H with molecule weight 30,03[1]. Formaldehyde with small condition and soluble in water easy to cross the cell membrane and absorbed by body. Formaldehyde has been produced by cells in metabolism of serine, glycine, methionine and coline. Environmentally, formaldehyde usually found in cigarette, paint, diesel, gasoline exhaust, medical and industrial products[2].

Formaldehyde has quick reaction with pollutants in the air but it has short reaction under the influence of sunlight. In solution, formaldehyde is able to bind amino acids like: lysine (K), arginine (R), tyrosine (Y), asparagine (N), histidine (H), glutamine (Q) and serine (S). While, in formaldehyde metabolism, it will be changed to be format acid by formaldehyde dehydrogenase in mitochondria and cytosol, then it will be excreted by kidney and as CO_2 by lung. Formaldehyde is also a reactive compound which enables to bind with macromolecules in which one of them is protein. Due to the binding protein by formaldehyde causing protein damage, so it can reduce the protein function. Dysfunctions protein interfere metabolic processes of the body and induce several diseases such as cancer, teratogenicity, neurodegenerative and vascular disorders[3].

Formaldehyde which binds with protein and DNA enable to form methylene bridges and produces covalently cross-linked complexes[1]. Formaldehyde that is soluble in water can diffuse easily into the blood vessels. It usually occurs in dialysis or in surgery that require circulation assistance[4].

This process occurs because of dialysis machine and tubes are disinfected with formaldehyde. Therefore, formaldehyde from adsorption can enter the patient's blood stream. The purposes of this study is to reveal the molecular mechanism of formaldehyde in human cancer cell.

MATERIALS AND METHODS

Materials: Formalin compund was retrieved form PubChem. PubChem[5,6] (http://pubchem.ncbi.nlm.nih.gov) is a public repository of chemical structures and associated biological activities. It was launched as part of the Molecular Libraries Roadmap[7] from the National Institutes of Health (NIH), which aims to increase the discovery and use of chemical probes through high-throughput screening of small molecules[7,8]. It is composed of three interconnected databases. The compound database contains unique chemical structures. The substance database contains batch/sample level descriptions of these chemical structures. The compounds used in the study of formaldehyde and formaldehyde SMILE structure downloaded in this program with accession number CID:712.

Protein compound interaction: The information of interact between formaldehyde with proteins was analyzed by using STITCH. The STITCH is a database of protein-chemical interactions that integrates many sources of experimental and manually curated evidence with text-mining information and interaction predictions. Available at http://stitch.embl.de, the resulting interaction network includes 390.000 chemicals and 3.6 million proteins from 1.133 organisms[9]. Finally, protein sequences can be submitted to find similar proteins in the database. Enter the SMILE with SMILE of formaldehyde, then select Go to be in the running by the program automatically. There are 10 protein that interaction with formaldehyde, they are DHRS4, AOC3, ALDH3A1, ADH5, FOS, TRPA1, DMGDH, SARDH, PIPOX and SHMT2.

Protein-protein interaction: The biological process, molecular function and cellular component of ten proteins was analyzed by using STRING. The STRING contains a unique scoring-framework based on benchmarks of the different types of associations against a common reference set, integrated in a single confidence score per prediction. The graphical representation of the network of inferred, weighted protein interactions provides a high-level view of functional linkage, facilitating the analysis of modularity in biological processes. The database predicts functional interactions at an expected level of accuracy of at least 80% for more than half of the genes; it is online at http://www.bork.embl-heidelberg.de STRING/[10]. Ten proteins that interact with formaldehyde has been found from STITCH program are inserted into the STRING program, select running go with the program automatically.

Pathway analysis: Base on the result from STRING program for function from founded proteins and we find the protein pathway which work in cancer cycle. The pathway of protein can induce cancer was analyzed by using KEGG. The KEGG pathway (http://www.genome.jp/kegg/pathway.html) has been widely used as a reference knowledge base for understanding biological pathways and functions of cellular processes. Pathways are stored and presented as graphs on the KEGG server side, where nodes are mainly molecules (protein, compound, etc.) and edges represent relation types

between the nodes e.g., activation or phosphorylation. The graph nature of pathways raised our interest to investigate them with powerful tools implemented in R and bioconductor[11,12] e.g., graph, RBGL and Rgraphviz[13].

RESULTS

Interact results from STICTH obtained show that formaldehyde can interact with 10 different proteins, they are DHRS4, AOC3, ALDH3A1, ADH5, FOS, TRPA1, DMGDH, SARDH, PIPOX and SHMT2 (Fig. 1). Evidence for specific actions from FOS protein and formaldehyde interaction are activation and expression which indicated by yellow and gray line. As for evidence for specific actions from TRPA1 protein and formaldehyde interaction are activation which indicated by gray line. While the other protein have evidence for specific actions as catalys which indicated by purple line.

Generally these proteins have important functions in the body, include biological processes, molecular function and cellular component. The SARDH, PIPOX and DMGDH have importent role in glycine metabolic process, serine family amino acid metabolic process, alpha-amino acid metabolic process, organic substance metabolic process and primary metabolic process and cellular process. The SARDH and SHMT2 also interacted with FOS for methylation. The PIPOX and SHMT2 also take a role in cellular modified amino acid metabolic process and cofactor metabolic process.

The FOS with ALDH3A1 take role in response to extracellular stimulus, response to organic and nitrogen compound, positive regulation of biological process. The ALDH3A1 have function in positive regulation of cell proliferation.

Fructooligosaccharide with ADH5 take a role in catabolic proces, response to molecule of bacterial origin, response to lipopolysaccharide, response to biotic stimulus and single-organismm development process. Biocare[14], ADH-5 Breast Marker Cocktail (Atypical Ductal Hyperplasia) is composed of CK5+CK14+p63+CK7+CK18 antibodies. This multiples cocktail can be used in a wide range of applications for breast cancer.

All of the protein have function the important role in cancer. Not only one, but they also interacted with other to do any process in cellular metabolism. So formaldehyde that bind with these protein can doubt the protein and also biological process, mollecular function and cellular component.

DISCUSSION

Fructooligosaccharide protein has many function in three biological processes and molecular function include DNA methylation, double-stranded DNA binding and transcription regulatory region DNA binding. Formaldehyde can increase the risk of cancer either by damaging DNA or by increasing the number of cell replications or both. Cell replication can rise

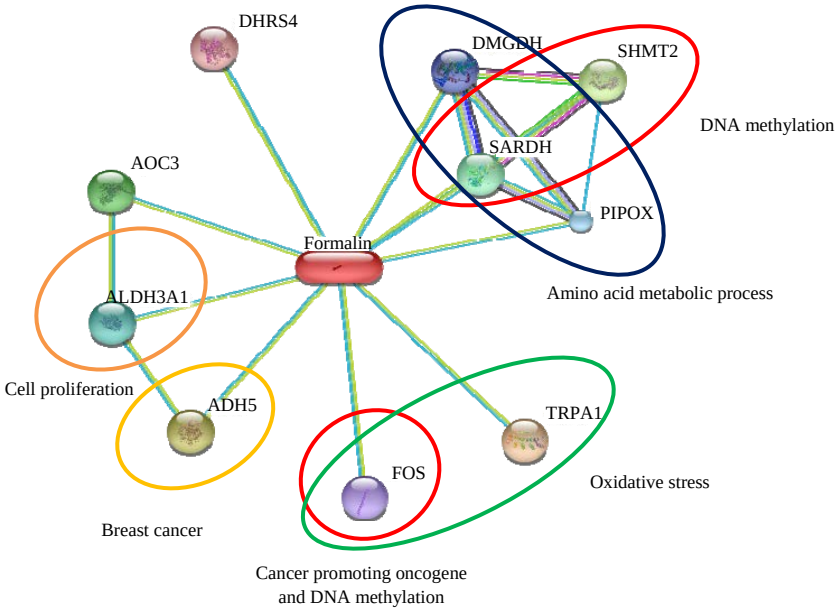

Fig. 1: Interaction of formaldehyde with 10 proteins that have role ın cancer, red circle: DNA methylation, blue: Amino acid metabolic process, green: Oxidative stress, yellow: Breast cancer, orange: Cell proliferation[22]

due to increased cell division (by mitogenesis), due to inhibited apoptosis or by regeneration processes following cytotoxicity. Whether genotoxicity is caused by an endogenous process or due to exogenous exposure leading to genetic changes, DNA replication is required to fix the genetic errors permanently. Thus, DNA replication not only provides more opportunities for errors, but also fixes the errors into a permanent genomic alteration. An increased DNA replication can lead to an increased risk of cancer. Even for genotoxic chemicals, the dose response for tumor incidence is essentially dependent on cell proliferation[15].

Formaldehyde exposure is associated with key events related to carcinogenicity, such as DNA reactivity, gene mutation, chromosomal breakage, aneuploidy, epigenetic effects (binding to lysine residues of histones), glutathione depletion, oxidative stress and cytotoxicity-induced cellular proliferation[16-18]. Formaldehyde exposure can cause cancer of the nose and sinuses in humans, as well as some types of leukemia and lymphoma. Formaldehyde is regulated as a carcinogen by Cal/OSHA and Cal/EPA[19]. Specific actions from FOS protein and formaldehyde interaction indicated that this interaction can induced the FOS protein can be converted into a cancer-promoting oncogene, because this protein interacted with some foreign compund.

The FOS and Jun proteins form the transcription factor activating protein 1 (AP-1). They play a role in cell proliferation and sustained angiogenesis in cancer pathway (Fig. 2). The FOS protein including FOS proteins (c-Fos, Fos B, Fra-1, Fra-2). They are can only form heterodimers with members of the Jun family. The c-Fos and Fos B expression was significantly lower than in the respective primary ovarian carcinomas[20]. The existence of formaldehyde which binds to the FOS protein causes decrease in the number of proteins in the cell, thereby triggering the cells into oncogene.

The FOS have role in response to calcium ion, if the formaldehyde bind with FOS it will be doubt the homeostasis of altered Ca^{2+}, cation and ion channel activity. According to IARC[19], formaldehyde exerts dose-dependent toxicity in cell cultures. Cytotoxicity involves loss of glutathione, altered Ca^{2+}-homeostatis and impairment of mitochondrial function. Thiols, including glutathione and metabolism through alcohol dehydrogenase 3, act in a protective manner.

Marcato *et al.*[21] more recently, experiments with murine hematopoietic stem cells, murine progenitor pancreatic cells and human breast Cancer Stem Cells (CSCs) indicate that other ALDH isoforms, particularly ALDH1A3, significantly contribute to aldefluor positivity, which may be tissue and cancer specific. ALDH1A3 function in Retinoic Acid (RA) cell signaling via RA production by oxidation of all-trans-retinal and 9-cis-retinal (map 05200). This function in particular has been linked to the "Stemness" characteristics of CSCs. Therefore, it is discussed that, increasing evidence indicates that ALDH may be more than just a CSC marker and have a potential functional role in CSC biology.

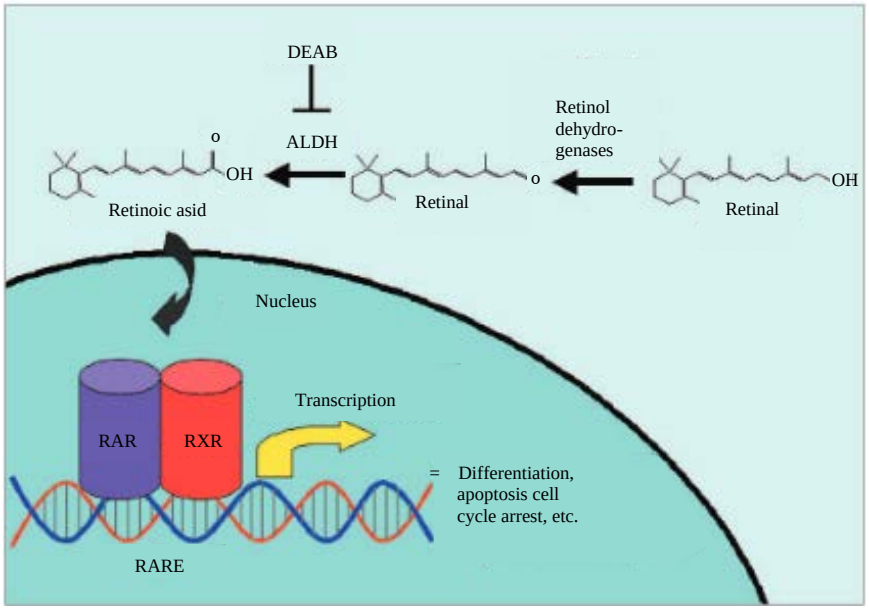

Fig. 2: Role of ALDH (ALDH3A1) in retinoic acid signaling[21]

CONCLUSION

Formaldehyde can interact with ten proteins (DHRS4, FOS, DMGDH, ALDH3A1, SARDH, AOC3, ADH5, SHMT2, PIPOX and TRPA1). The existence of formaldehyde which binds to the FOS protein causes decrease in the number of proteins in the cell, thereby triggering the cells into oncogene. The interaction between formaldehyde and these protein can distrub the biological process, molecular function and cellular component in human.

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