Computational Proteome-Wide Study for the Prediction of Escherichia coli Protein Targeting in Host Cell Organelles and Their Implication in Development of Colon Cancer

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ABSTRACT: Enterohemorrhagic Escherichia coli infection is associated with gastrointestinal disorders, including diarrhea and colorectal cancer. Although evidences have established the involvement of E. coli in the growth of colon cancer, the molecular mechanisms of carcinogenesis of cancer growth and development are not well understood. We analyzed E. coli protein targeting in host cell organelles and the implication in colon cancer using in silico approaches. Our results indicated that many E. coli proteins targeted the endoplasmic reticulum (ER), ER membranes, Golgi apparatus, Golgi apparatus membranes, peroxisomes, nucleus, nuclear membrane, mitochondria, and mitochondrial membrane of host cells. These targeted proteins in ER, Golgi apparatus, peroxisomes, nucleus, and mitochondria may alter the normal functioning of various pathways including DNA repair, apoptosis, replication, transcription, and protein folding in E. coli-infected host cells. The results of the current in silico study provide insights into E. coli pathogenesis and may aid in designing new preventive and therapeutic strategies.

1. INTRODUCTION

Cancer is a big health challenge to the global populations. Lung cancer is diagnosed as the most common cancer in both sexes and the major cause of death followed by breast cancer, prostate cancer, colon cancer, stomach cancer, and liver cancer. Recent evidence suggests that bacteria may contribute to the growth and development of various human cancers.\(^ 2\)\(^ 3\) Colorectal cancer (CRC) is the third most common cancer diagnosis and the second deadliest malignancy in males and females.\(^ 4\) Various factors are involved in colon cancer growth. The contribution of Escherichia coli in the etiology of colon cancer may be due to its promotion of chronic inflammation in the colon.\(^ 5\) E. coli is connected to the development of colitis, which is a possible risk factor for colon cancer.\(^ 6\)\(^ 7\) The diseases of the colon due to E. coli-mediated chronic inflammation include ulcerative colitis, inflammatory bowel disease, and Crohn’s disease-induced colon cancer.\(^ 8\)\(^ 9\)\(^ 10\) Host cells with these inflammatory conditions are colonized by enteroinvasive E. coli (EIEC), which has the potential of growth in the internal environment of the cell.\(^ 11\)\(^ 12\) E. coli employs various strategies that enable the growth and development of CRC. The epidemiologic connection between EIEC and colon cancer is established. Recent reports have confirmed that colonization with E. coli is involved in the development of colitis and colon cancer.\(^ 7\)\(^ 10\)

Polyketide synthase (PKS) pathogenicity islands increase the risk for E. coli-mediated development of colon cancer. The gene encoding PKS pathogenicity islands are responsible for the regulation of several important metabolites, including colibactin. Deletion of the PKS genes in E. coli decreased DNA damage and neoplastic lesions in IL10\(^ {−/−}\) mice colonized with E. coli.\(^ 13\) The oncogenic potential of colibactin of E. coli B2 phylogenetic group strain has been confirmed.\(^ 14\) Complete molecular studies of E. coli at the time of intracellular infection are needed. This may involve the induction of inflammatory diseases in colon cancer. E. coli proteins may work as components of the host cell proteome, and E. coli targeting of subcellular components alters the normal functioning of the host cells. Many novel insights have been made regarding the possible involvement of pathogenic strains of E. coli in colon cancer etiology. E. coli may alter several pathways responsible for the growth of colon cancer in susceptible persons. Proteins targeting intracellular pathogens in host cells play important

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roles in host cell regulation, including cell growth and apoptosis. Bioinformatics tools are very important for the predictions of subcellular localization of proteins, structure of proteins, and function of different proteins. The isoelectric point (pI) of particular protein is the pH on which a protein carries zero net charge. The pI of specific enzymes or protein is important to understanding their biochemical utility and therefore analyzing the value of pI is a key aspect of proteomic studies. Numerous essential cellular processes are controlled in subcellular compartments of the host cell, including the nucleus, endoplasmic reticulum (ER), Golgi complex, and peroxisomes. E. coli proteins may adversely influence these compartments. Recent studies demonstrate that proteins targeting various bacterial proteomes in the nucleus, cytoplasm, ER, and mitochondria are implicated in cancer progression, including prostate, lungs, and colon cancers. We analyzed the E. coli proteins targeting subcellular organelles, including the ER, Golgi complex, peroxisomes, nucleus, mitochondria, and cytoplasm, of the host cell that are implicated in the growth and development of colon cancer using bioinformatic approach.

2. RESULTS

2.1. Selection of Protein Database of E. coli. We have selected EcoProDB, which contains 561 E. coli proteins. These were used to predict E. coli protein targeting of subcellular organelles in E. coli-infected host cells.

2.2. Analysis of Subcellular Targeting of E. coli Proteins by LocTree3. LocTree3 predicted subcellular protein targeting in 18 classes of eukaryotes. The strategies used to predict protein targeting in subcellular organelles are illustrated in Figure 1. The diagram demonstrates the example of one of the proteins targeting the nonmembranous secretory pathway in the ER with an expected accuracy of 0.99 using an advanced profile kernel support vector machine (SVM). The results for the 561 E. coli proteins targeting organelles in the host cells are summarized in Table 1. LocTree3 analyses demonstrated that the highest number of proteins targeted by E. coli was located in the cytoplasm, followed by the mitochondrion. Lower numbers of proteins were targeted in other organelles, including the ER (3), ER membranes (4), Golgi apparatus membranes (3), mitochondrial membranes (11), nucleus (24), peroxisomes (9), plasma membranes (10), vacuole (3), and vacuole membranes (2). The results of the current protein targeting prediction study were demonstrated graphically in Figure 2. Descriptions and functions of the proteins targeting the ER, ER membranes, Golgi complex, Golgi complex membranes, peroxisomes, and peroxisome membranes are displayed in Table 1.

These subcellular organelles are dynamic and believed to be important for intracellular transportation and play a role in the growth of cancer. The ER is important for the regulation of housekeeping functions and maintaining homeostasis within the cell. When the normal functioning of the ER is disrupted, a phenomenon known as “ER stress” stimulates pathways to counteract this disruption, collectively termed the unfolded protein response (UPR). The UPR is associated with the growth of cancer due to chronic stress and alteration in the normal phenomenon of programmed cell death. Similarly, various E. coli proteins target the Golgi complex, Golgi complex membranes, peroxisomes, and peroxisome membranes affecting the normal functioning of the host cell and inducing carcinogenesis. Complete descriptions of subcellular

Table 1. Prediction of E. coli Protein Targeting in Subcellular Organelles of Host Cells by LocTree 3.0 Predictor

| s. no. | sub-cellular organelles | no. of proteins targeted |
|-------|-------------------------|----------------------------|
| 1     | chloroplast             | 92                         |
| 2     | chloroplast membrane    | 01                         |
| 3     | cytoplasm               | 210                        |
| 4     | ER                      | 03                         |
| 5     | ER membrane             | 04                         |
| 6     | Golgi apparatus membrane| 03                         |
| 7     | mitochondrion           | 103                        |
| 8     | mitochondrion membrane  | 11                         |
| 9     | nucleus                 | 24                         |
| 10    | peroxisome              | 09                         |
| 11    | plasma membrane         | 10                         |
| 12    | plastid                 | 04                         |
| 13    | secreted                | 69                         |
| 14    | vacuole                 | 03                         |
| 15    | vacuole membrane        | 02                         |

Figure 1. Scheme illustrated the E. coli protein targeting which may promote the growth of colon cancer.
protein targeting and their functions in bacterial cells are illustrated in the Supporting Information (Table S1).

2.3. Isoelectric Point Value and Molecular Weight of E. coli Proteins. Proteins targeting the lumen of the ER had $M_w$s between 18.2 and 43.9 kD and pI values between 5.1 and 5.5 predicted with up to 84% expected accuracy. Proteins targeting the ER membrane had $M_w$s between 34.7 and 64.5 kD and pI values between 5.1 and 5.5 predicted with 84% expected accuracy (Table 2). Nine proteins targeted peroxisome interiors and had $M_w$s between 20 and 56 kD and pI values between 4.7 and 6.3 predicted with 93% expected accuracy (Table 3). Proteins with $M_w$s between 9.1 and 24.9 kD and pI values between 4.55 and 9.75 were found to target the cytoplasm of host cells. The expected accuracy for proteins targeting the cytoplasm of host cells typically decreased with increasing $M_w$s. The E. coli proteins targeting the cytoplasm of host cells may disturb the normal physiology of the cell. The results of our work showed the highest number of E. coli proteins targeting the cytoplasm of the host cells. Three hundred and three proteins were predicted to target the mitochondria and eleven proteins targeted the mitochondrial membrane. Twenty-four proteins were predicted to target the nuclear interior. Descriptions of these proteins are in the Supporting Information (Table S1).

3. DISCUSSION

Possible factors in cancer progression include radiation, chemical carcinogens, inflammation, tobacco, mutations, diet, and infections. Among these, infections are associated with approximately 16% of cancers. Bacterial infections are associated with the growth of cancers through abnormal functioning of various pathways in host cells. Bacterial infections were originally not believed to be cancer promoters. However, the association between the growth of bacteria and cancer has been confirmed. Various bacterial proteins are related to cancer etiology. The gut microbiota may be involved in the progression of CRC through various strategies and mechanisms. E. coli is a crucial bacteria of the human intestinal microbiota, but some pathogenic E. coli strains may induce chronic inflammatory responses and produce various toxins, including cyclomodulins, which may be involved in carcinogenesis. We employed the latest version of LocTree3 which used advanced analyses and SVMs, including a fast, novel SVM profile kernel (16,17); insertion of annotation transfer-derived homologs and experimentally annotated localization by BLAST (12); caching of results for faster processing in repeated searches (19,20); and gene ontology annotations for calculation of outcomes (18).

Subcellular protein targeting demonstrated reliability, which was quantified by percentage-expected accuracy. Cyclomodulin-positive pathogenic strains of E. coli are found more commonly on mucosal membranes of CRC patients than on mucosal membranes of healthy individuals. Previous studies confirmed that various nuclear targeting E. coli proteins are involved in the growth of colon cancer in host cells. The group proteins known as cyclomodulins have the ability to modulate the cell cycle of the host. Cyclomodulins create breaks in double-stranded DNA in host cells and direct the progression of colon cancer. We focused on nonnuclear targeting E. coli proteins during infection. Proteins with high $M_w$s targeted the interior of the ER and ER membranes with more than 80% expected accuracy (Table 2). Quinoprotein glucose dehydrogenase (P15877), ADP-1-glycero-0-manno-heptose-6-epimerase (P67910), and chain length determinant protein (P76372) targeted the interior of the Golgi apparatus membrane (Table 3). These proteins may alter normal protein folding in host cells and contribute to the progression of colon cancer. Accretion of unfolded E. coli proteins in the ER and ER membranes may trigger ER stress and encourage cleavage of ATF6 that subsequently directs the activation of UPR genes (Figure 2). Activation of UPR has been connected to the growth of colon cancer. Golgi fragmentation was recognized in cancer more than fifty years ago. Studies of peroxisome proteins and metabolites support their pro-tumorigenic functions through alterations in peroxisome receptors. Many of these proteins are toxins involved in the growth of cancer in affected host cells. Detailed information, and the
| accession no. | protein name                                      | mol. weight (dalton) | pI value | protein targeting results using LocTree3 expected accuracy (%) | functions in bacteria                                                                 |
|--------------|--------------------------------------------------|----------------------|----------|---------------------------------------------------------------|----------------------------------------------------------------------------------------|
| P0A9X4       | rod shape-determining protein MreB               | 36 952.4             | 5.19     | ER                                                           | involved in the formation of the rod shape of the cell. May act as a negative regulator of PtsI |
| P24232       | Flavohemoprotein                                 | 43 867.66            | 5.48     | ER                                                           | involved in nitric oxide (NO) detoxification in anaerobic processes, termed nitric oxide dioxygenase (NOD) reaction that utilizes \( \text{O}_2 \) and \( \text{NAD(P)}^+ \) \( \text{H} \) to convert NO to nitrate, which protects the bacterium from various noxious nitrogen compounds. Induced by NO (under aerobic conditions), nitrate, nitrate (under anaerobic conditions), nitroso compounds, and paraquat. Induced by low pH during anaerobic growth |
| P23869       | peptidyl-prolyl cis-trans isomerase B             | 18 153.47            | 5.51     | ER                                                           | see PpiA                                                                                   |
| P0AB77       | 2-amino-3-ketobutyrate coenzyme A ligase         | 43 117.04            | 5.64     | ER membrane                                                 | negatively regulated by Lrp                                                                  |
| P3687        | hypothetical ABC transporter ATP-binding protein YadG | 34 647.07            | 8.44     | ER membrene                                                 | not available                                                                               |
| P6075        | lipid A export ATP-binding/permease protein MsbA | 64 460.71            | 8.62     | ER membrane                                                 | involved in lipid A export and possibly also in glycerophospholipid export and for biogenesis of the outer membrane |
| PO2942       | methyl-accepting chemotaxis protein I            | 59 442.99            | 4.88     | ER membrene                                                 | not available                                                                               |
| P67510       | ADP-\( \beta \)-glycero-\( \beta \)-manno-heptose-6-epimerase | 34 893.17            | 4.8      | Golgi apparatus membrane                                    | catalyzes the interconversion between ADP-\( \beta \)-glycero-\( \beta \)-manno-heptose and ADP-\( \beta \)-glycero-\( \beta \)-manno-heptose via an epimerization at carbon 6 of the heptose. Completely inhibited by ADP and ADP-glucose and partially inhibited by ATP and NADH. It is induced by heat shock |
| P76372       | chain length determinant protein                 | 36 454.74            | 5.43     | Golgi appp ratus membrane                                   | confers a modal distribution of chain length on the O-antigen component of lipopolysaccharide (LPS). Gives rise to a reduced number of short-chain molecules and increased numbers of longer molecules |
| P1587        | quinoprotein glucose dehydrogenase               | 86 747.35            | 5.4      | Golgi appp ratus membrane                                   | may be involved in energy conservation rather than in sugar metabolism                       |
| Protein Name | Accession No. | Molecular Weight (Da) | pI Value | Expected Accuracy (%) | Functions |
|--------------|--------------|-----------------------|----------|------------------------|-----------|
| L-lactate dehydrogenase | P33232 | 72,619 | 6.33 | 93 | Enzyme involved in L-lactate metabolism. |
| NADH dehydrogenase | P0A6F3 | 99,571 | 5.36 | 86 | Component of the respiratory chain, involved in oxidative phosphorylation. |
| Glycerol kinase | P0ABU0 | 63,087 | 5.99 | 82 | Key enzyme in glycerol metabolism, involved in the regulation of glycerol uptake. |
| Naphthoate synthase | P0ABH7 | 63,087 | 5.07 | 80 | Converts O-succinylbenzoyl-CoA to 1,4-dihydroxy-2-naphthoic acid. |
| Putative Nudix hydrolase | P65566 | 56,827 | 4.7 | Not available | |
cytoplasm of host cells would provide a binding site for the regulation of protein synthesis.

Studies have demonstrated that increased expression of heat shock proteins (HSPs) are related to the growth and development of cancer. HSPs are involved in various aspects of carcinogenesis, including cell differentiation, cell proliferation, invasion, cell death, immune recognition, and metastasis. We predicted various cytoplasm-targeting HSPs, including chaperone protein HchA (P31658), 33 kDa chaperonin (P0A6YS), universal stress protein G (P39177), and trigger factor (P0A850), are necessary for proper protein folding in stress situations. Several bacterial HSPs have adverse effects in humans at the cellular level. Conversely, several bacterial HSPs protect epithelial cells from apoptosis and help to increase cell proliferation through the regulation of ERK and MAP kinase. HSPs are highly conserved proteins, for example, Hsp70 has approximately 50% sequence similarity between humans and E. coli. The most highly conserved sequences may be 96% similar across species. The early reports have revealed that the infection of a pathogenic strain of E. coli decreases or alters the expression of various tumor suppressors and oncogenes which may act as a potential factor for carcinogenesis through the induction of cellular proliferation. The BAX protein is considered as a strong factor to control the pro-apoptotic activities. BAX is usually dispensed in the cytoplasm of cells or loosely connected with the membrane of mitochondria. Upon stimulation of apoptosis, BAX is induced to undergo conformational change and regulate the normal functioning of apoptosis. Downregulation in the expression of BAX alters the normal phenomenon of apoptosis by the regulation of activation of caspase proteases. Therefore, different proteins of E. coli in various subcellular organelles play an important role in the growth of colon cancer.

4. CONCLUSION AND FUTURE WORK
The connection between E. coli and colon cancer is established. However, the E. coli target or E. coli linked factor, contributing to the progression of colon cancer, remains unknown. We concluded that various E. coli proteins targeting subcellular organelles of host cells play an important role in the growth of colon cancer. Although various prominent factors are associated with the growth of colon cancer but the infection with E. coli and their protein targets could not be ignored. Our results indicated that 24 E. coli proteins targeted into the nucleus of host cells. Therefore, future research should help to identify the potential functions of each protein. Some of these proteins may be pathogen-secreted host nuclear proteins, and then focus will be on studying the interactions between these proteins and host cells. In near future, the selected proteins may be used as a target vaccine eliciting an immune response against the E. coli and CRC. Available literature demonstrates that various toxins, such as cyclomodulin, have altered the normal functions of host cells. Additionally, we reported that E. coli proteins targeted the ER, ER membrane, Golgi apparatus, and peroxisomes, and this may be connected with the growth of colon cancer through abnormal pathway functioning. Alteration of ER and Golgi environments results in Golgi fragmentation that substantially alters the functions of residential Golgi glycosyltransferases and leads to the development of cancer-specific glycosyl epitopes. Alteration in the expression of oncogenes and tumor suppressor genes potentially associated with the growth of colon cancer. Emerging research in bacterial protein targeting in host cells confirms that E. coli protein targeting is a dynamic factor in the growth of colon cancer.

5. EXPERIMENTAL SECTION OR COMPUTATIONAL METHODS
5.1. Selection of E. coli Proteins Database. We utilized the E. coli protein database (EcoProDB) supported by the Korean Advanced Institute of Science and Technology (KAIST). This database contains 561 E. coli proteins with descriptions available from Swiss-Prot and the E. coli cell envelope protein data collection. In near future, the selected proteins may be used as a target vaccine eliciting an immune response against the E. coli and CRC. Available literature demonstrates that various toxins, such as cyclomodulin, have altered the normal functions of host cells. Additionally, we reported that E. coli proteins targeted the ER, ER membrane, Golgi apparatus, and peroxisomes, and this may be connected with the growth of colon cancer through abnormal pathway functioning. Alteration of ER and Golgi environments results in Golgi fragmentation that substantially alters the functions of residential Golgi glycosyltransferases and leads to the development of cancer-specific glycosyl epitopes. Alteration in the expression of oncogenes and tumor suppressor genes potentially associated with the growth of colon cancer. Emerging research in bacterial protein targeting in host cells confirms that E. coli protein targeting is a dynamic factor in the growth of colon cancer.
system uses kernel-based SVMs and homology-based inference to analyze native subcellular protein targeting in eighteen classes of eukaryotes, six classes of bacteria, and three classes of Archaea. LocTree3 predicted three localization classes: three in Archaea (plasma membrane, cytoplasm, and extracellular), six in bacteria (plasma membrane, cytoplasm, periplasmic space, outer membrane, fimbrium, and extracellular), and eighteen in Eukaryota (nucleus, nuclear membrane, cytoplasm, ER, ER membranes, mitochondria, mitochondrial membrane, Golgi apparatus, Golgi membranes, peroxisomes, peroxisome membranes, vacuole, vacuole membranes, chloroplast, chloroplast membrane plastids, plasma membranes, and extracellular). The scheme of prediction of protein targeting of E. coli in different subcellular organelles of the host cell and their implication in growth of cancer are shown in Figure 3.

### 5.3. Isoelectric Point Value and Molecular Weight of E. coli Proteins

Isoelectric point (pI) values and molecular weight (Mw) of E. coli proteins were predicted by ExPASy using the compute pI/Mw tool. This computational tool predicts the theoretical pI and Mw from a list of UniProt Knowledgebase (Swiss-Prot or TrEMBL) entries or for user-sequenced entries. 38

### ASSOCIATED CONTENT

#### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.9b04042.

Analysis of E. coli proteins targeting in various subcellular organelles of the host cell and their potential functions in bacterial cells (PDF)

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#### Notes

The authors declare no competing financial interest.

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