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ORIGINAL ARTICLE

Computational prediction of *Mycoplasma hominis* proteins targeting in nucleus of host cell and their implication in prostate cancer etiology

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Abstract Cancer has long been assumed to be a genetic disease. However, recent evidence supports the enigmatic connection of bacterial infection with the growth and development of various types of cancers. The cause and mechanism of the growth and development of prostate cancer due to *Mycoplasma hominis* remain unclear. Prostate cancer cells are infected and colonized by enteroinvasive *M. hominis*, which controls several factors that can affect prostate cancer growth in susceptible persons. We investigated *M. hominis* proteins targeting the nucleus of host cells and their implications in prostate cancer etiology. Many vital processes are controlled in the nucleus, where the proteins targeting *M. hominis* may have various potential implications. A total of 29/563 *M. hominis* proteins were predicted to target the nucleus of host cells. These include numerous proteins with the capability to alter normal growth activities. In conclusion, our results emphasize that various proteins of *M. hominis* targeted the nucleus of host cells and were involved in prostate cancer etiology through different mechanisms and strategies.

Keywords *Mycoplasma hominis* · Protein targeting · In silico · Host nucleus · Prostate cancer · Etiology

Abbreviations

M. hominis	*Mycoplasma hominis*
ORFs	Open reading frames
NLS	Nuclear localization signal or sequence
BaCeILo	Balanced subcellular localization
LGT	Lateral gene transfer

Introduction

Evidence has shown the possible role of bacterial infection in the growth and development of various types of cancer etiologies including colon cancer, lung cancer, and prostate cancer [1–3]. Although the accurate mechanism behind this connection is not clear, the inflammation caused by bacteria is supposed to be a potential factor behind this enigmatic connection. Mycoplasmas are a heterogeneous group of microbes competent for self-replication for their growth. Cell-wall-free mycoplasmas can cause several diseases in animals including urogenital and respiratory diseases in humans [4, 5]. The most common species of mycoplasma recognized in the urogenital tract of humans are *Mycoplasma hominis* (*M. hominis*), *Mycoplasma genitalium*, and *Ureaplasma urealyticum*. Initially, the association of mycoplasmas with human malignancy was observed in the 1960s [6]. Various reports have described the significant association of *M. hominis* infection with the progression and development of prostate cancer [3, 7, 8]. The enigmatic connection emerged to be significant

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through the statistical analysis of *M. hominis* infection with the progression of a higher category of prostate cancer.

The infection of mycoplasma is not only associated with damaged DNA but also linked with the alteration of checkpoints of the cell cycle that regulate normal cell division and the process of programming cells during apoptosis by offering potent modified cell growth signals [9]. Many continuous signals could be transferred to infected cells through the close interaction of mycoplasmas with host cells' surfaces, which may lead to chronic alteration in the expression of different genes. Therefore, these enigmatic changes in the infected host cells affect several important biological processes including the control of cell growth [9, 10]. It is estimated that about 20 % of all types of cancers in humans originate from chronic infection or chronic inflammatory states [11]. Chronic inflammation leads to the stimulation of pro-inflammatory cytokines and highly reactive oxygen species that result in chlorination and nitration in DNA, RNA, and different proteins [11, 12]. Although *M. hominis* infection is connected with an increased risk of prostate cancer, several other factors are also involved in the growth and development of prostate cancer [11, 13]. In addition to mutation in DNA and chronic inflammation, various cyclomodulins have been determined in the progression of prostate cancer mediated by *M. hominis*. Cyclomodulins have the potential to modulate the normal checkpoint of the host cell cycle, and it has been supposed that they have evolved as etiological factors for *M. hominis*-induced prostate cancer [9]. *M. hominis* is a common extracellular gram negative pathogen, but it replicates and colonizes intracellularly in the progression of prostate cancer [14]. This unusual colonization of *M. hominis* in the genital tract including the prostate may have specific implications in the etiology of prostate cancer. The whole genome of *M. hominis* (collected by American Type Culture Collection as ATCC 27545) contains approximately 715,165 base pairs (bp) with 26.94 % G+C content. The complete genome of *M. hominis* comprises 563 open reading frames (ORFs) which encode various proteins and enzymes.

Many bacteria are susceptible to intracellular infection and replication in the cells of a particular host, where they alter the normal functioning of infected cells by targeting their proteins in various organelles of the host cells including the nucleus, mitochondria, cytoplasm, and plasma membrane (secretory protein) [14, 15]. During the intracellular replication of *M. hominis* infection, various proteins are targeted in the host cell and these proteins may act as a part of the host cell. In these situations, different proteins of *M. hominis* have the possible chance to localize in the host cell compartments due to the existence of signature sequences and evolutionary relatedness for protein targeting in the cellular organelles of host cells. The aim of this study is to predict the protein targeting of *M. hominis* in host cells to decipher the enigmatic role in prostate cancer etiology, with a specific focus on the nuclear-targeting protein through bioinformatics tools. The proteins of *M. hominis* may have exerted many effects on the different pathways of host cells and may act as a risk factor lesion to prostate cancer growth and development. In the present study, we identify the *M. hominis* proteins targeting the mitochondria and cytoplasm of host cells and investigate the potential role, involvement, and associations of *M. hominis* proteins in prostate cancer etiology.

Materials and methods

The complete proteome of *M. hominis* was used for the prediction of subcellular localization in the host cell nucleus and the possible role in prostate cancer etiology.

Selection of the *M. hominis* protein database

The Universal Protein Resource (UniProt) database of *M. hominis* was used to predict the protein targeting in this study. The UniProt database is a comprehensive resource for protein sequences and annotation data. This database was formed by the collection of the Swiss-Prot, TrEMBL, and PIR protein database activities [16]. The UniProt database includes vast information on *M. hominis* proteins and their subcellular location as mentioned in Swiss-Prot/TrEMBL or PIR-PSD [17–19]. Two proteomes of *M. hominis* strains, ATCC-23114/PG21 and ATCC-27545, were available in the UniProt database [20]. The whole proteome of the ATCC-27545 strain of *M. hominis* was selected for the prediction of the nuclear localization signal (NLS) and human cell subcellular localization in host cells using a cNLS mapper and balanced subcellular localization (BaCeILo) predictors. NLS is a sequence of amino acid known as nuclear localization signal or sequence which "tags" a protein for transfer into the nucleus of cell through specific nuclear transport. Generally, the sequence of NLS consists of one or more than one short signal with positively charged arginine and/or lysine residues existed on the surface of protein. Various nuclear targeted proteins may share the identical NLS. The NLS can be classified into two types, classical and non-classical. Furthermore, classical NLSs (cNLSs) can be categorized into monopartite and bipartite NLS on the basis on the number of cluster of basic amino acids separated by spacer amino acids. The amino acid sequence PKKKRKV was discovered the first monopartite NLS.

Prediction of the NLS in the *M. hominis* proteins

The cNLS mapper was used for the prediction of NLSs in the entire protein sequence [21]. Both monopartite and bipartite NLSs were predicted in *M. hominis* proteins for eukaryotic cells. The proteins of *M. hominis* with specific cutoff values,

1–2, 5–3, 7–8, and 8–10, were predicted as exclusively localized to the cytoplasm, both the nucleus and the cytoplasm, partially localized to the nucleus, and absolutely localized to the nucleus, respectively, as described in the available information on cNLS. In order to predict nuclear localization, the uppermost cutoff values of the NLS were analyzed in *M. hominis* proteins. Proteins indicating transitional NLS cutoff values were listed as per their specific ranges (e.g., the cutoff value 5.5 or above was included with 7–8, while 5.4 or below was included with 3–5).

Prediction of nuclear localization in the *M. hominis* proteins by BaCeILo

The BaCeILo predictor was used to predict nuclear localization in the proteins of *M. hominis* for host eukaryotic cells. BaCelLo, a powerful bioinformatics tool, is based on different support vector machines (SVMs) organized into a decision tree for the prediction of subcellular localization in five compartments, namely the cytoplasm, nucleus, mitochondrion, secretory protein (plasma membrane), and chloroplast [22]. This predictor can predict the potential targeting of specific proteins in three kingdoms: animals, plants, and fungi. In this study, we analyzed protein subcellular targeting in the animal kingdom and the *M. hominis* protein as the query sequence.

Results

Selection of the *M. hominis* protein database

The selection of the UniProt consortium was due to its valuable properties such as a comprehensive, entirely classified, opulent, and more accurately annotated protein sequence database, with broad cross-references and query interfaces. The complete proteome of the ATCC-27545 strain of *M. hominis* was downloaded from the UniProt database, as it contains the highest proteins (563) in comparison with other strains (only 529 proteins). Various proteins of *M. hominis* in host cells may alter the normal functioning of cells and may direct to the growth of cancer.

Prediction of the NLS in the *M. hominis* proteins

The cNLS mapper predicted the location of proteins in the cytoplasm, both the nucleus and the cytoplasm, partially in the nucleus, and exclusively in the nucleus of host cells. Monopartite as well as bipartite NLSs was predicted in *M. hominis* proteins to predict eukaryotic NLSs. A total of 99 *M. hominis* proteins were found to have monopartite NLSs. Among those, 7, 15, 59, and 18 proteins were observed to have 8–12, 7–6, 5–3, and 2–1 cutoff values for NLSs, respectively. Moreover, the bipartite NLS was observed in 556 proteins of *M. hominis*. This comprised 15, 158, 390, and 17 proteins with 10–8, 7–6, 5–3, and 2–1 cutoff values for NLSs, respectively.

Prediction of nuclear localization in the *M. hominis* proteins by BaCeILo

Out of the 563 *M. hominis* proteins, only 29 were found to target the host cell nucleus through the prediction of BaCeILo. The results of the prediction analysis revealed the detail on *M. hominis* protein subcellular localization in different compartments of the host such as 320 cytoplasmic, 77 mitochondrial, 29 nuclear, and 137 secretory proteins. Increasing the NLS cutoff values of both monopartite and bipartite raises nuclear targeting (up to a cutoff value of 5.0), while the reverse is seen above a 5.0 cutoff value (Table 1). Although no exact correlation was found between molecular weight and nuclear targeting, 60–80 kDa molecular weight proteins were mostly targeted to the host cell nucleus (Table 2). Furthermore, isoelectric point (p*I*) values did not show any constant pattern for nuclear targeting (Table 3). The patterns of *M. hominis* protein targeting in the host cell nucleus with different parameters are illustrated in Fig. 1. In addition, the protein targeting patterns of all *M. hominis* proteins with different parameters are illustrated in Fig. 2. Most nuclear-targeting proteins were identified to be involved in various steps of DNA replication and gene expression. The complete descriptions of the results of the nuclear-targeting proteins with their functions are revealed in supplementary Table S1.

Tran and Wente (2006) confirmed that proteins of <40 kDa molecular weight can pass into the nucleus through passive transport [23]. In this study, we predicted the possible targeting of *M. hominis* proteins with a molecular weight <40 kDa through the BaCeILo predictor. It was found in our study that 333 out of 563 proteins of *M. hominis* have molecular weights <40 kDa, but their localization was not always predicted as nuclear.

Discussion

Prostate cancer is the second most commonly diagnosed malignancy and the sixth leading cause of death due to cancer globally. The incidence of prostate cancer has steadily increased in the populations of Asian countries including China, India, and Malaysia [13]. The growth and development of cancer due to bacterial intracellular infection requires the detection of its protein targeting to host cell compartments. The localization of bacterial proteins in the host cell compartments including the nucleus has a great effect on cancer etiology [24]. These proteins can regulate several aspects of host cells, including normal growth behavior. Chronic inflammation connected with infections has been identified as an

Table 1 Computational prediction of *M. hominis* proteins targeting to the nucleus of host cells and their relation with all proteins with a similar NLS

NLS	NLS cutoff	Number of proteins targeting nucleus	Total number of proteins in this range	Percentage
Monopartite NLS	0–3.0	23	509	4.51
	3.0–5.0	5	32	15.63
	5.0–8.0	1	16	6.25
	>8.0	0	6	0
Bipartite NLS	0–3.0	2	76	2.63
	3.0–5.0	16	290	5.52
	5.0–8.0	11	194	5.67
	>8.0	0	3	0

important cancer-promoting factor in several cancers, including prostate cancer [11, 25–27]. The detection of more chronic infections connected with cancer and the mechanisms essential for cancer-promoting activity will be crucial for the development of novel approaches for cancer treatment, prevention, and identification [25]. The potential association of *M. hominis* infection with the growth and development of prostate cancer requires the prediction of its protein targeting in different compartments of host cells. Targeting various proteins of *M. hominis* in the host cell can have a significant effect on prostate cancer etiology. The targeted proteins can control many features of infected host cells, including altering the normal behavior of growing cells [3, 7]. Although several experimental high-throughput approaches have been developed for the determination of protein localization, they are neither cost effective nor time saving [28]. Various bioinformatics tools for predicting the subcellular targeting of proteins are an attractive complement to the experimental process [29, 30]. These tools mostly work on either similarity/alignment search or the identification of a particular sequence motif essential for the localization of a specific protein [21, 29]. We emphasized predictors using diverse principles for predicting the subcellular targeting of proteins to get important information from different methods.

The nuclear targeting of any protein is a key event to control the normal functioning of host cells. It is usually predicted by finding the particular motifs of the protein sequence known as NLSs [31]. Diverse tools are developed to predict these particular motifs in sequence. Six classes of NLSs have been identified in which the nuclear import of proteins is mediated by the α/β pathways of importin. The best explained nuclear import receptor is the dimer of α and β importin. The importin α acts as a potential adapter protein that binds the cNLS, which is recognized by either one (monopartite NLS) or two (bipartite NLS) enriched basic stretches of amino acids [32]. The possible activity of NLS sequences alters within the same NLS class with alterations in the NLS sequence [33, 34]. Hence, we particularly employed an NLS mapper in our study, which predicts NLS activity as an alternative to the NLS sequence based on the involvement of each amino acid residue in NLSs; this should offer more acceptable prediction performance [21, 33]. Furthermore, the NLS mapper detects the activity of an NLS as a separate peptide instead of the complete structural context of a native protein.

BaCeILo was also used in our study for the prediction of the subcellular targeting of *M. hominis* proteins in host cells. The BaCeILo predictor works on different SVMs systematized in a decision tree, and it analyzes nuclear, mitochondrial, cytoplasmic, secretory protein, and chloroplast targeting of particular query proteins [22]. It utilizes complete sequences as well as the N and C termini of protein sequences for testing,

Table 2 Computational prediction of *M. hominis* proteins targeting to the nucleus of host cells and their relation with all proteins with similar molecular weight

Molecular weight	Number of proteins targeting to nucleus	Total number of proteins	Percentage
0–20 kD	7	128	5.47
20–40 kD	13	205	6.28
40–60 kD	2	109	1.84
60–80 kD	4	61	6.56
>80 kD	3	60	5.00

Table 3 Computational prediction of *M. hominis* proteins targeting to the nucleus of host cells and their relation with all proteins with a similar p*I* value

Range of p*I* value	Number of proteins targeting to nucleus	Total number of proteins	Percentage
3.0–5.0	2	25	8
5.0–6.0	5	105	4.77
6.0–7.0	1	68	1.47
7.0–8.0	1	35	2.86
8.0–9.0	6	109	5.51
9.0–10	12	181	6.63
10.0–11.0	1	33	3.03
11.0–13.0	1	7	14.29

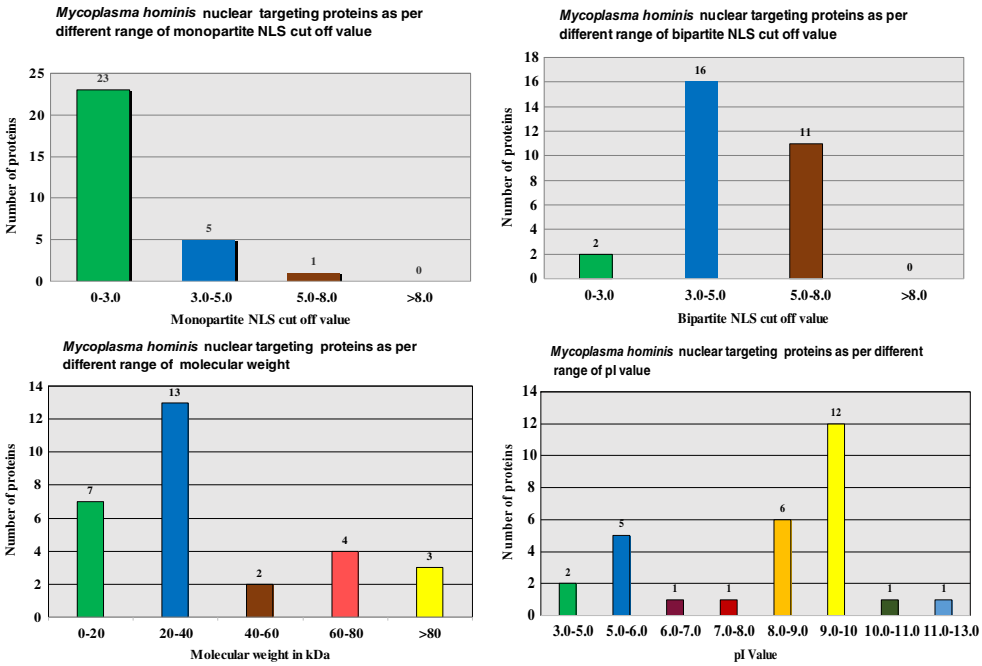

Fig. 1 Computational prediction of *M. hominis* proteins targeting the nucleus of host cells and their relation with various parameters

and it analyzes the results found based on evolutionary information and amino acid sequence by alignment. Therefore, BaCeILo and the NLS mapper analyze sequences in different ways. The NLS mapper analyzes the protein sequence based

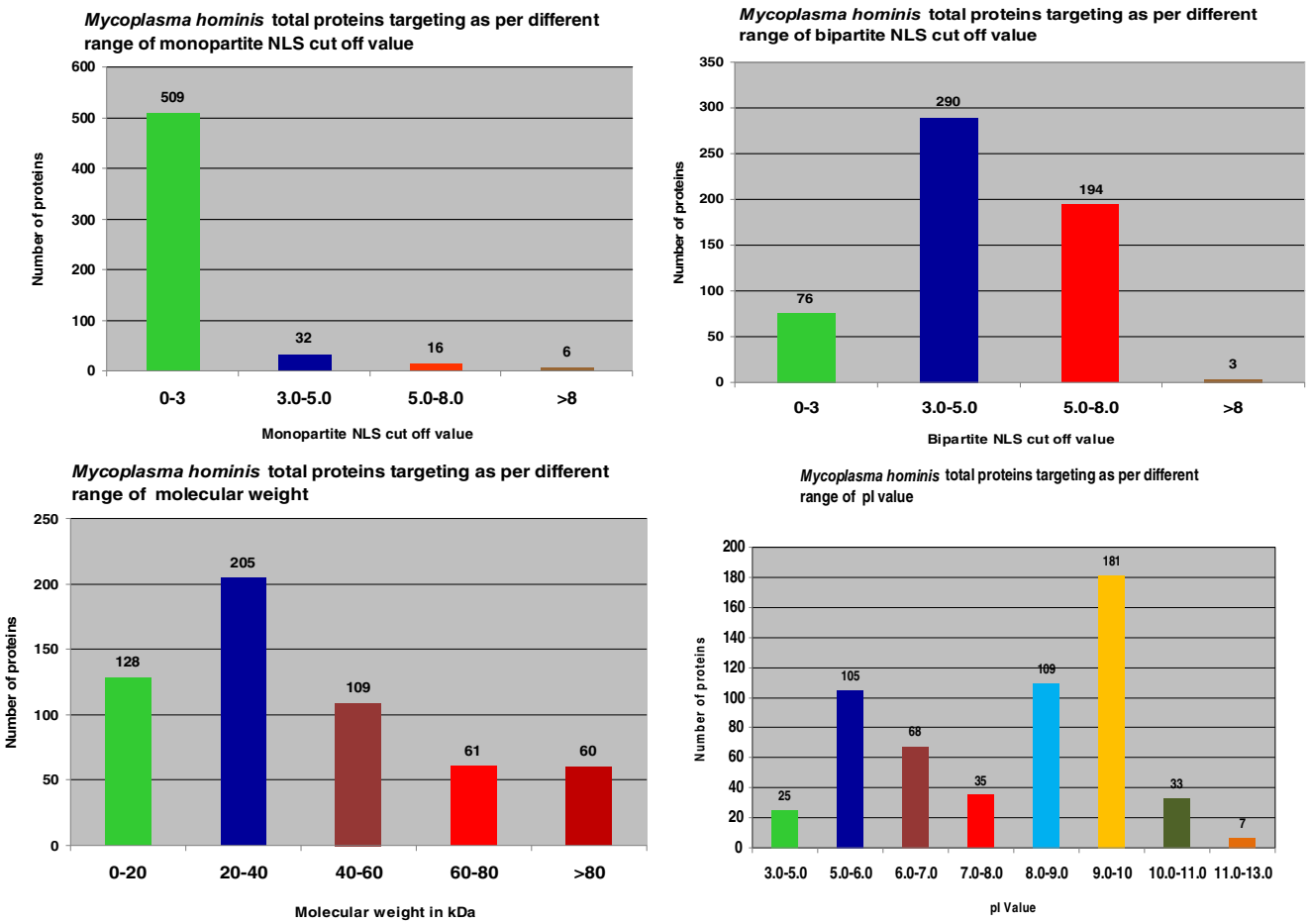

Fig. 2 Computational prediction of all the proteins of *M. hominis* (UniProt database) and their relation with various parameters

on available data produced from yeast. Although it is a eukaryotic sequence-based predictor, its ability to analyze NLSs in human proteins is questionable. Therefore, the development and advancement of more appropriate human-specific NLS predictors can resolve such a problem. We also applied the BaCeILo predictor to analyze the nuclear targeting of *M. hominis* proteins besides NLSs. This is based on diverse principles as discussed above. Presently, it is identified that approximately 30 % of nuclear proteins contain actual NLSs [22, 35]. These findings suggest that a huge number of proteins transfer to the nucleus even with a lack of NLSs. Moreover, the nuclear targeting of proteins <40 kDa molecular weight has been discussed above by passive modes. Thus, the variations in targeting through two different predictors are reasonable, but the obtained results should be confirmed in wet labs prior to any conclusions being drawn. In addition, we emphasized the possible effects of these nuclear-targeting proteins of *M. hominis* on the growth and development of cancer.

Nuclear targeting of the *M. hominis* proteins and their potential roles in prostate cancer etiology

Among the 563 proteins of *M. hominis* present in the UniProt database, just 29 proteins were analyzed to target the nucleus of host cells during the intracellular colonization of *M. hominis*. However, 563 proteins were part of the whole proteome of *M. hominis*. Thus, more advanced research can provide novel results and new information about the proteome of *M. hominis* and the possible implications in the control of the various pathways of host cells.

Involvement of replication and DNA-binding proteins

Genomic instability is an important factor in cancer susceptibility; however, its potential mechanism in the progression and development of cancer remains unclear. An earlier study showed that *M. hominis* has the ability to suppress p53 and activate NF-kappaB during infection [36]. A frequently stated hypothesis is that abnormalities in translesion DNA synthesis or error-prone phenotypes in DNA replication cause instability in genomic DNA and are thus a prominent source in the progression of cancer. It is recognized that mutations in DNA replication proteins are enigmatically connected with the development of varieties of cancers in humans, although the regulated process of replication is essential for the proliferation of normal cells [37]. Various DNA-binding proteins are involved in the growth and development of cancers. For instant, Parry and Clarke (2011) showed that the methyl CpG-binding protein alters the methylation of target DNA that can be involved in the growth and development of cancer [38]. Similarly, DNA damage-binding protein 2 is an important protein of nucleotide excision repair, and impairing its activity is proposed as a potential cause of cancer [39].

In the same way, chromodomain helicase DNA-binding protein 5 is also called a repressor of tumor progression, and damage to its function due to mutation has been identified as a possible cause of breast cancer [40]. Our results revealed various proteins with nucleotide- or DNA-binding properties in *M. hominis* that are found to target the nucleus of host cells (Supplementary table S1). Therefore, the simultaneous existence of *M. hominis* and host DNA-binding proteins in prostate cells provides hints for the possible involvement of DNA-binding proteins in prostate cancer etiology. Both proteins of the host and pathogen have common substrates; therefore, the possibility of the competitive binding of such proteins with substrates is expected. The binding of bacterial proteins can reduce the binding of normal host proteins to the binding site of DNA. The growth and development of several tumors may be associated with a variety of inhibitors of DNA-binding proteins. Another class of proteins is inhibitors of DNA-binding proteins in humans, which are involved in the regulation of programmed cell death and normal cell cycles. It has been illustrated that the overexpression of these inhibitors of DNA-binding proteins is connected with the progression of ovarian cancer [41]. The *M. hominis* protein RpoD (A0A097NT29) and chromosome partition protein Smc (A0A097NTX2) are examples of DNA-binding proteins targeting the nucleus of host cells as observed in our prediction study.

DNA repair proteins

The *M. hominis* protein DNA topoisomerase is involved in the repair of DNA. Homologs of DNA topoisomerase also exist in human beings, but it is certain that the same enzymes from two different organisms do not have comparable activity. Considering these facts, it can be assumed that DNA topoisomerase activity will compete with its homolog present in humans. Our study predicted that *M. hominis* DNA topoisomerase (A0A097NST8) targets the nucleus of host cells, where it can reduce or completely inhibit the activity of DNA repair proteins in humans. It has been suggested that bacteria has the capability to decrease host cell mismatch DNA repair in cancer patients [42]. *M. hominis* infection was also exhibited to act as an oncogene able to cooperate with H-ras or c-myc to induce transformation and cause the growth of cancer [43]. Certainly, many regulators are present in *M. hominis* that can alter the normal functioning of the DNA repair of the host cell. The above demonstration of the reduced mismatch repair activity in *M. hominis*-infected cells demands a legitimate appraisal to assess the potential of *M. hominis* DNA topoisomerase in host cell DNA repair. Bacterial DNA topoisomerase and host cell DNA topoisomerase work on the same substrate; therefore, both can compete with each other to generate mutations, which may promote the growth and development of cancer.

Possible role of gene expression regulators in cancer growth and development

Alterations in the interaction of transcriptional and/or translation regulators associated with the growth and development of cancer are caused by the dysregulation of many critical genes. It is confirmed that the dysregulation of many crucial genes directs the activation of proto-oncogenes and the suppression of anti-oncogenes in bacteria [44]. Conserved nature in structural resemblances within different RNA polymerase subunits and antigenicity are the characteristics of eukaryotes. The results of our study indicated that the RNA polymerase sigma factor (A0A097NT29) of *M. hominis* targeted the nucleus of host cells, which can alter the normal functioning of RNA polymerase. However, this situation needs experimental validation prior to drawing any conclusions regarding the possible involvement of the *M. hominis* RNA polymerase subunit in the regulation of human gene expression. The transcription of the DNA sequence of humans, called an arrest site for RNA polymerase II, by bacterial RNA polymerase discloses that bacterial enzymes can work efficiently with this DNA [45]. Present knowledge about the transcription termination of eukaryotic is very restricted, but it has been suggested that few genes transcribed through the polymerase II of eukaryotes utilize attenuation and anti-termination mechanisms related to bacteria [46].

In silico prediction results have their own limitations, and experimental evidence is essential to confirm the actual role of transcriptional regulators or their subunits targeting the nucleus of host cells. Currently, it is logical to suggest that the *M. hominis* RNA polymerase subunit targets the nucleus of human cells, which can exert a significant impact on the expression of various genes. Alteration in gene expression is a major feature for the development of cancer [47], and *M. hominis* RNA polymerase may be involved in prostate cancer etiology by this mechanism [48]. However, our prediction study is based on only 563 proteins (whole proteome) of *M. hominis*. Therefore, further research can collect more information about the localization of other *M. hominis* proteins to the host nucleus and their possible connections with gene expression in humans. It can be supposed that the various transcription and translation regulators of *M. hominis* can migrate to the host nucleus and may be involved in the alteration of host gene expression.

In addition to transcriptional regulators, several other *M. hominis* proteins such as ribosomal RNA small subunit methyltransferase H (A0A097NT42), ribosome-recycling factor (A0A097NTW3), 30S ribosomal protein S2 (A0A097NTZ2), 50S ribosomal protein L2 (A0A097NTB6), 30S ribosomal protein S3 (A0A097NT97), 30S ribosomal protein S5 (A0A097NTA2), and many other proteins could target the nucleus (supplementary table S1). The majority of such targeting proteins play a significant role in the control of gene expression. Therefore, the result of our study shows the possible involvement of *M. hominis* colonization and infection and their effectors in protein nuclear targeting in the etiology of prostate cancer.

Possible role of lateral gene transfer in cancer etiology

The phenomenon of lateral gene transfer (LGT) is the transfer of DNA/RNA by ways other than direct vertical transfer through parents to their offspring. It has been observed that the process of LGT from bacteria to humans is a general event in the development of cancer [49]. The somatic cells of humans are inhabited in huge microbiota that comprises about 10^{14} bacterial cells that outnumber (10 to 1) human cells [49]. Many human cells are in a regular and close relationship with the existing microbiome, and many eukaryotes including humans have widespread LGT from bacteria [50]. It has been suggested that LGT from bacteria to eukaryotes including humans can have various implications in the etiology of cancer [51]. The intracellular colonization of *M. hominis* in prostate cancer cells offers a strong clue for the potential involvement of *M. hominis*-induced LGT in prostate cancer etiology. As discussed above, various *M. hominis* proteins/enzymes have homologs with human proteins/enzymes. It can be assumed that these particular DNA sequences will also be homologous in both *M. hominis* and humans. Therefore, the possibilities of LGT can be enhanced when two homologous sequences exist in the same cell. Although our study is based on the presently known proteome of *M. hominis* (563 proteins), scientific advancement linked with collecting further knowledge and information regarding all *M. hominis* proteins can provide us with more accurate targets for *M. hominis*-induced prostate cancer etiology. This finding may also be valuable to plan management strategies and find a cure for prostate cancer.

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Compliance with ethical standards

Conflicts of interest None

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