Original article

Prediction of *Chlamydia pneumoniae* protein localization in host mitochondria and cytoplasm and possible involvements in lung cancer etiology: a computational approach

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**Abstract**

Collecting evidence suggests that the intercellular infection of *Chlamydia pneumoniae* in lungs contributes to the etiology of lung cancer. Many proteins of *Chlamydia pneumoniae* outmanoeuvre the various systems of the host. The infection may regulate various factors, which can influence the growth of lung cancer in affected persons. In this in-silico study, we predict potential targeting of *Chlamydia pneumoniae* proteins in mitochondrial and cytoplasmic comportments of host cell and their possible involvement in growth and development of lung cancer. Various cellular activities are controlled in mitochondria and cytoplasm, where the localization of *Chlamydia pneumoniae* proteins may alter the normal functioning of host cells. The rationale of this study is to find out and explain the connection between *Chlamydia pneumoniae* infection and lung cancer. A sum of 183 and 513 proteins were predicted to target in mitochondria and cytoplasm of host cell out of total 1112 proteins of *Chlamydia pneumoniae*. In particular, many targeted proteins may interfere with normal growth behaviour of host cells, thereby altering the decision of program cell death. Present article provides a potential connection of *Chlamydia pneumoniae* protein targeting and proposed that various targeted proteins may play crucial role in lung cancer etiology through diverse mechanisms.

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1. Introduction

Lung cancer is one of the main reasons for cancer-related mortalities world-wide (Siegel et al., 2016). The association of *Chlamydia pneumoniae* (*C. pneumonia*) infections with lung cancer etiology has been previously suggested (Byrne and Ojcius, 2004; Laurila et al., 1997). However, the process of carcinogenesis is not well understood yet. *C. pneumoniae* is a widespread intracellular respiratory bacterium that needs host cell for their existence and multiplication within host cells. It has evolved various effector proteins and toxins that interfere with cell death signalling pathways in host cells and the machinery of cell death executioner (Bohme and Rudel, 2009). Nucleus, mitochondria, and cytoplasm are critical components for normal host-cell functions (Bhavsar et al., 2007; Hess et al., 2003). Mitochondria, which are generally considered to originate from endosymbiotic event, plays an important role in numerous biochemical cascades that direct to programmed cell death (Gray et al., 1999). Therefore, investigating the mechanisms by which intracellular pathogens such as *C. pneumoniae* may alter apoptotic pathways is of special interest.

We have recently studied the nuclear targeting of *C. pneumoniae* proteins through computational approach during intracellular infection where they may play crucial role in progress and development of lung cancer (Khan et al., 2016a). Nevertheless, the fact that many *C. pneumoniae* proteins are targeted into mitochondria, cytoplasm, and other host intracellular components may alter many biochemical pathways in the host. Here we systematically predict several *C. pneumoniae* proteins that can localize into host...
mitochondria and cytoplasm where they can influence the development and progress of lung cancer.

2. Materials and methods

2.1. Protein database for the selection of C. pneumoniae strain

The Uniprot database was screened out for the selection of C. pneumoniae strain. Five strains C. pneumoniae are publicly accessible in Uniprot database with different number of proteins (Kalman et al., 1999; Myers et al., 2009; Read et al., 2000; Shirai et al., 2000). The C. pneumoniae pathogen is reported as obligate gram negative bacteria which may act as a potential factor of lung cancer (Yang et al., 2003; Zhan et al., 2011).

2.2. cNLS mapper for the analysis of NLS

The bioinformatics software cNLS mapper was utilized for the analysis of nuclear localization signal (NLS) in whole proteins of C. pneumoniae TW-183 strain (Kosugi et al., 2009a). The whole sequence of all proteins was utilized for the analysis of monopartite and bipartite NLS sequence cutoff value.

2.3. BaCelLo for the analysis of sub cellular protein targeting in different cell compartments

Protein targeting of C. pneumoniae TW-183 stain in different eukaryotic cell organelles were analysed by bioinformatics software Balanced Sub Cellular Localization predictor (BaCelLo). The BaCelLo software based on three well known datasets for eukaryotic kingdoms which includes plants, fungi, and animals (Pierleoni et al., 2006). The software analyses the five different classes of sub cellular localization such as mitochondrial, cytoplasmic, nuclear, chloroplast and secretory. The current study was performed with animal data sheet related tool.

3. Results

3.1. Protein database for the selection of C. pneumoniae strain

Whole proteins of C. pneumoniae (TW-183 strain) were analysed in present study. We selected C. pneumoniae TW-183 strain for our prediction study because of its contains the largest proteome, total of 1112 proteins, as compared to the other four C. pneumoniae strains J138, CWT029, AR39 and LPcoLN (Kalman et al., 1999; Myers et al., 2009; Read et al., 2000; Shirai et al., 2000). Scheme showed the summary of work plan for data analysis and possible outcome. Detailed description was presented in the experimental, result and discussion section (Fig. 1).

3.2. Prediction of mitochondrial targeting of C. pneumoniae proteins

The prediction results of BaCelLo have shown 183 proteins targeted to host cell cytoplasm out of total 1112 proteins of whole C. pneumoniae proteome. Most of the proteins containing NLS cutoff value of 3–5 were targeted to the cytoplasm with respect to monopartite NLS and bipartite NLS cutoff values (Table 1). Also, most proteins with higher molecular weights were associated host-cell cytoplasmic localization with few exceptions (Table 2).

3.3. Prediction of cytoplasmic targeting of C. pneumoniae proteins

The prediction results of BaCelLo have shown 513 proteins targeted to host cell cytoplasm out of total 1112 proteins of whole C. pneumoniae proteome. The outlines of proteins localization in host mitochondria illustrated in Fig. 2. Furthermore, as shown in (Table S1), we have provided details about 183 proteins predicted to target mitochondria during our study.

4. Discussion

Various bacterial proteins modulate host cell survival leading to dynamical suppression of host cell death as a mean for bacterial persistence and multiplication (Fan et al., 1998; Fischer et al., 2001; Rajalingam et al., 2001; Ballestar and Esteller, 2005. In silico analysis of protein subcellular localization can significantly help to explain bacterial–protein potential functions. Although many advanced experimental high-throughput approaches have been developed to determine proteins localization, they are time consuming and cost ineffective (Huh et al., 2003; Khan et al., 2016b, 2016c; Laurila and Vihinen, 2009; Mote and Reines, 1998).

In the advancement of bioinformatics, fast and highly-accurate genome-scale computational predictors of subcellular protein targeting/localization offer a good complement for experimental practice (Garg et al., 2005; Reinhardt and Hubbard, 1998). cNLS Mapper predicts classical NLS functionality of proteins by analysing summation of the functional role of each amino acid in the query protein as per the activity-based profiles, which are achieved from the systematic residue-replacement analyses in Saccharomyces cerevisiae. Although analysis of NLS in a particular sequence of protein is essential for analysing its nuclear localization with the highest cNLS score, the cNLS Mapper is a predictor to analyse NLS activity rather than NLS sequence as it consequently predicts cytoplasmic localization of proteins (Hahn et al., 2008; Kosugi et al., 2009a, 2009b).

In contrast, BaCelLo is another predictor that utilizes a decision tree which was developed on diverse SVMs for the prediction of nuclear, mitochondrial, chloroplast, and cytoplasmic targeting of particular proteins (Pierleoni et al., 2006). Also, BaCelLo predicts complete protein sequence along with its N and C termini and analyse the results on the basis of information gained by amino acid residue sequence and evolutionary alignment. To impede different mitochondrial functions, bacterial proteins should attach to and enter the mitochondria during the course of infection (Cossart and Sansonetti, 2004; Kozjak-Pavlovic et al., 2008). In addition to several anomalous mitochondrial functions, cancer cells have impaired oxidative phosphorylation as a result of the high-rate modified glycolysis with elevated fermentation of lactic acid, which permits cancer cells to retain biosynthetic fluxes at the time of fast proliferation (DeBerardinis et al., 2008; Rudel et al., 2010;
Table 1
Computational prediction of Chlamydia pneumoniae proteins targeting to mitochondria and cytoplasm of host cell and their relation with total proteins with similar NLS.

| NLS          | NLS Cutoff values | Number of proteins targeting mitochondria | Total number of proteins in this range | Percentage NLS Cutoff values | Number of proteins targeting cytoplasm | Total number of proteins in this range | Percentage |
|--------------|-------------------|-------------------------------------------|----------------------------------------|-----------------------------|----------------------------------------|----------------------------------------|------------|
| Monopartite NLS | 0–3.0             | 151                                       | 981                                    | 15.39                       | 465                                    | 981                                    | 47.40      |
|              | 3.0–5.0           | 13                                        | 64                                     | 20.31                       | 22                                     | 64                                     | 34.27      |
|              | 5.0–8.0           | 16                                        | 50                                     | 5.0–8.0                     | 17                                     | 50                                     | 34         |
|              | >8.0              | 3                                         | 17                                     | >8.0                        | 9                                     | 17                                     | 52.94      |
| Bipartite NLS | 0–3.0             | 24                                        | 274                                    | 8.75                        | 108                                    | 274                                    | 39.41      |
|              | 3.0–5.0           | 109                                       | 616                                    | 17.69                       | 305                                    | 616                                    | 48.51      |
|              | 5.0–8.0           | 48                                        | 209                                    | 5.0–8.0                     | 93                                     | 209                                    | 44.49      |
|              | >8.0              | 2                                         | 13                                     | >8.0                        | 0                                     | 13                                     | 53.84      |

Table 2
Computational prediction of Chlamydia pneumoniae proteins targeting to mitochondria and cytoplasm of host cell and their relation with total proteins with similar molecular weight.

| Molecular weight | Number of proteins targeting to mitochondria | Total number of proteins | Percentage Molecular weight | Number of proteins targeting to cytoplasm | Total number of proteins | Percentage |
|------------------|-----------------------------------------------|--------------------------|-----------------------------|-------------------------------------------|--------------------------|------------|
| 0–20 kD          | 65                                            | 326                      | 19.93                       | 0–20 kD                                  | 326                      | 31.28      |
| 20–40 kD         | 67                                            | 384                      | 17.44                       | 20–40 kD                                 | 384                      | 49.73      |
| 40–60 kD         | 36                                            | 235                      | 15.31                       | 40–60 kD                                 | 235                      | 53.61      |
| 60–80 kD         | 10                                            | 87                       | 11.49                       | 60–80 kD                                 | 87                       | 64.36      |
| >80 kD           | 5                                             | 80                       | 6.25                        | >80 kD                                   | 80                       | 47.50      |

Table 3
Computational prediction of Chlamydia pneumoniae proteins targeting to mitochondria and cytoplasm of host cell, and their relation with total proteins with similar pl value.

| Range of pl value | Number of proteins targeting to mitochondria | Total number of proteins | Percentage Range of pl value | Number of proteins targeting to cytoplasm | Total number of proteins | Percentage |
|-------------------|-----------------------------------------------|--------------------------|-----------------------------|-------------------------------------------|--------------------------|------------|
| 3.0–5.0           | 4                                             | 106                      | 3.77                        | 3.0–5.0                                   | 58                       | 4.71       |
| 5.0–6.0           | 22                                            | 297                      | 7.40                        | 5.0–6.0                                   | 187                      | 62.96      |
| 6.0–7.0           | 20                                            | 175                      | 11.42                       | 6.0–7.0                                   | 96                       | 54.85      |
| 7.0–8.0           | 10                                            | 79                       | 12.65                       | 7.0–8.0                                   | 38                       | 48.10      |
| 8.0–9.0           | 24                                            | 150                      | 16                          | 8.0–9.0                                   | 59                       | 29.33      |
| 9.0–10            | 61                                            | 215                      | 28.37                       | 9.0–10                                    | 52                       | 24.18      |
| 10.0–11.0         | 30                                            | 70                       | 42.85                       | 10.0–11.0                                 | 17                       | 24.28      |
| 11.0–13.0         | 12                                            | 20                       | 60                          | 11.0–13.0                                 | 6                        | 30         |
Wallace, 2012). Nevertheless, cancer cells showed antagonistic properties towards mitochondria-mediated apoptotic pathways (Sabharwal and Schumacker, 2014; Wallace, 2012). In the current in silico analysis, we predicted a sum of 183 proteins out of total 1112 proteins of *C. pneumoniae* targets to host-cell mitochondria, which may alter mitochondrial functions to the favour of oncogenesis.

We analysed bacterial DNA-binding protein HU due to its potential of influencing mitochondrial protein expression. As they share properties with histone proteins, the potential involvement of DNA-binding proteins in the growth and progression of cancer have been revealed in various studies. Methyl CpG binding protein has the potential to interfere with methylation of target DNA and involved as a crucial factor for the progression of cancer (Ballestar and Esteller, 2005; Ghoshal and Bai, 2007). Chromodomain helicase DNA binding protein 1-like (CHD1L) plays a critical role in pathogenesis of hepatocellular carcinoma (Clemencon et al., 2013; Li et al., 2013). Similarly, Chromodomain helicase DNA binding protein 5 (CHD5) is an effective tumor repressor that potentially engaged in the growth of lung cancer due to their function inactivation by epigenetic mechanism (Silvera et al., 2010; Zhao et al., 2012). In general, bacterial DNA-binding proteins may interfere with ability of host DNA-binding proteins to interact with host DNA. It has been observed that over expression of inhibitor of DNA-binding protein (Id1) and vascular endothelial growth factor (VEGF) is associated with the growth and progression of various type of cancer (Georgiadou et al., 2014; Kubelac et al., 2014; Grzmil and Hemmings, 2012). Moreover, our findings show that many gene expression regulators can target host mitochondria. These proteins include, but are not limited to, transcription initiation factor sigma D protein (Q9Z811), transcription repressor protein HrcA (Q9Z850), endonuclease IV (Q9Z783), tRNA-ribosyltransferase (Q9Z88W5), DNA-directed DNA polymerase III chain (Q7VQ53), Methionyl-tRNA formyltransferase (Q9Z7Q5), DNA repair protein RecO (Q9Z7W5), Ribonuclease H-III (Q9Z61), ribosome-binding factor A (Q9Z8M0), RNA methyltransferase (Q9Z7N0), endonuclease III (Q9Z769), translation initiation factor IF-3 (Q9Z6R9).

Mitochondria have their own genetic material and proteinsynthesizing machinery, which more closely resembles bacteria. It has been examined in a study that bacterial RNA polymerase have the capability to act upon host DNA sequences due to conserved nature of RNA polymerase II and bacterial RNA polymerases (Kechavarzi and Janga, 2014; Mote and Reines, 1998). Another study illustrated conserved mechanisms for substrate binding and nucleotide integration with bacteriophage RNA polymerase (Kim and Lee, 2009; Schwinghammer et al., 2013). Similarly, the possible function of transcription termination proteins of *C. pneumoniae* on human transcription termination genes should be examined prior to any conclusion. Although enormous difference is observed among the mechanisms of transcription termination in human and bacterial cells, it is found plausible that many RNA polymerase II transcribed genes of eukaryotes use attenuation and antitermination processes as same as bacteria (Boland et al., 2013). Therefore, we predicted the localization of transcription termination associated factor IF-3 and DNA-directed DNA polymerase III chain in host mitochondria.

Moreover, the DNA-binding proteins we predicted may also interfere with other existing mitochondrial gene regulation proteins in host cells through binding with particular sequences as they may alter the expression level of various genes. Many reports revealed that alteration in the replication and/or expression of
mitochondria is connected with progression of many type of cancer including lung cancer (Giang et al., 2013; Shapovalov et al., 2011; Wang et al., 2015; Verstraeten et al., 2011). Mutations in the mitochondrial DNA (mtDNA) have long been supposed to play a crucial role in cancer etiology including lung cancer (Brandon et al., 2006). Earlier reports showed that approximately 43% of lung cancers had mtDNA mutations (Fliss et al., 2000). The mtDNA is more common for mutations because of reduced fidelity of DNA polymerase of mitochondria, increased level of generation of endogenous ROS, and lack of effective repair mechanisms for mtDNA (Maximo et al., 2009). Although our results revealed the potential of various C. pneumoniae proteins to enter host mitochondria and create mutation in host mtDNA and subsequently alter gene expression, the limited information of in silico studies required accurate experimental support prior to conclusion. Furthermore results with other proteins are illustrated in Table S1.

The metabolism of cancer cell characterized by elevated rate of glycolysis in presence of oxygen (Koppenol et al., 2011). This event, noticed by O. Warburg in 1924 and believed as the result of a “damaged” metabolism (Warburg, 1956). Our results indicated the inactivation of protoporphyrinogen oxidase, associated with liver cancer in acute porphryias (Schneider-Yin et al., 2015). Similarly, DNA methyltransferases performed the process of methylation and a potential targets for cancer therapy (Ghoshal and Bai, 2007). Moreover, ADP/ATP carrier protein 2 (Q9Z7U0) predicted in cytoplasmic localization, which act as a decisive component in apoptosis and demonstrated recently to have an important role in cancer (Clemencon et al., 2013). In addition, nucleoside diphosphate kinase (NDK) (Q9Z7TS), is also analysed to localize in the cytoplasm of host cell. NDK is involved in cell growth differentiation, proliferation, and tumor metastasis. Furthermore, it is also important for the metabolism and synthesis of nucleotide. The presence of enzyme NDK in host cytoplasm has been implicated in cancer etiology (Kimura et al., 2000). Nevertheless the exact role of NDK in cancer needs further appraisal. Thus, it might be possible that the expected future of a cell is dictated by various factors of host and microbiota, including bacteria, in order to transform a normal cell into cancerous cell.

Translation is a very important process to control the normal expression of several proteins. The possible involvement of translation-associated proteins in growth and advancement of cancer was examined and confirmed in numerous studies (Bhat et al., 2015; Ruggero, 2013). In our study, various ribosomal proteins of C. pneumoniae were predicted to localize in cytoplasm of host cell, which also acts as RNA-binding proteins. For instant, 305 ribosomal protein S1 (Q9Z8M3), S6 (Q9Z6V5), S5 (Q9Z7S), and S20 (Q9Z7F2) are needed to express the mRNA with Shine–Dalgarno sequence. Similarly, various 50S ribosomal proteins are predicted in our study including L10 (Q9Z92A), L9 (Q9Z6V3), L4 (Q9Z7Q8), L5 (Q9Z7R9), L29 (Q9Z7R5), L27 (Q9Z807), L33 (Q9Z8T4), L34 (Q9Z6X1) and L35 (Q9Z6R8), L36 (Q9Z6X0), which potentially involved in various steps of translation and ribosome biogenesis in C. pneumoniae. Control of translation is a critical component for the progress and advancement of cancer (Bhat et al., 2015; Silvera et al., 2010). It was reported that hyper-activated signalling pathways potentially manipulate the translation, which may be permitting of uncontrolled growth of cells (Grzmił and Hemmings, 2012). The cytoplasmic localization of C. pneumoniae enzymes and protein, which were observed in our study, showed the capability to interact with various regulatory elements and RNA of the host. Several RNA-binding proteins were shown to play a significant role in cancer development through regulation of gene expression at the post-transcriptional level (Grzmił and Hemmings, 2012; Kecharvazi and Janga, 2014). Many recent studies reported the involvement of various RNA-binding enzymes in cancer progression (van Kouwenhove et al., 2011; Wurth, 2012).

A category of enzymes are ribonucleases that cleave the phosphodiester bond of RNA and directing to many types of cellular consequences in host cell. It is evident that mammalian ribonucleases are involved in both prevention and development of various types of cancer (Kim and Lee, 2009). Nevertheless, the possible involvement of bacterial ribonucleases during their infection in oncogenesis is not much identified and requires precise biological corroboration. In our study, various ribonucleases such as ribonuclease III (Q9Z9C7), ribonuclease Z (Q9Z9G6), ribonuclease G (Q9Z9G9), and ribonuclease HIII (Q9Z9G62) were analysed to localize in cytoplasm of host cell. Ribonuclease III (Q9Z9C7) is involved in processing mRNA, rRNA, and tRNA, whereas ribonuclease Z (Q9Z9G6) is involved in 3′-tRNA processing activity. In addition,
ribonuclease HII (Q92962) and ribonuclease G (Q9Z6U9) are showing RNA-DNA hybrid ribonuclease activity in C. pneumoniae. Hence, ribonuclease-activated prodrugs emerged as a new line of investigation (Ellis et al., 2012). GTPase HfX (Q7VQ01) is another RNA-binding protein predicted in our study. GTPase have the ability to hydrolyse the GTP and potentially involved in infection-induced oncogenesis (Verstraeten et al., 2011). Nevertheless, further more suitable experimental validation for C. pneumoniae cytoplasmic localization in human and their potential role in lung cancer etiology.

Altered level of expression of heat shock proteins (HSP) in different types of cancer have been investigated in several studies (Calderwood and Gong, 2012; Calderwood et al., 2006). Here, we predicted the cytoplasmic localization of various conserved HSP including HSP-70 (P27542), 60 kDa chaperonin (GroEL protein (P31681), and Protein GrpE (HSP-70 cofactor) (Q9Z849), which may be engaged in accurate protein folding during adverse conditions in C. pneumoniae. For instant, Hsp70 shares about 50% sequence identity between C. pneumoniae and human whereas many domains showed 96% identities (Schlesinger, 1990; Zugel and Kauffman, 1999). It has been revealed in several reports that bacterial HSPs helps in protection of epithelial cells from apoptosis and may enhance the process of cell proliferation (Zhang et al., 2004, 2001). The involvement of bacterial HSPs in proliferation of cell and cytoplasmic targeting of C. pneumoniae HSPs in lung cells during infection enhance the possible risk of lung cancer. This potential association between C. pneumoniae infection and risk of lung cancer gained credibility in the past many years but no consensus has been reached.

5. Conclusion

Taken together, our current prediction results show that C. pneumoniae protein targeting host-cell mitochondria and cytoplasm may act as a potential factor for growth and development of lung cancer. We hypothesize that alteration in normal functioning of cells may induced the process of carcinogenesis due to host-pathogen protein–protein interaction through dysregulation in various pathways of mitochondria and cytoplasm with different strategies. Although the present research suggests explanations of the role of C. pneumoniae in the progress and advancement of lung cancer, experimental research are urgently needed to confirm and validate the in-silico results. These findings should open new avenues for clinical microbiologists and oncologists when dealing with C. pneumoniae infections.

Competing interests statement

The authors state no any competing interest related to present work.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jpsy.2017.05.007.

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P. Barman-Aksozen et al. / Saudi Pharmaceutical Journal 25 (2017) 1151–1157