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Research Article

Genetic Analysis of Nucleoside Diphosphate Kinase Variants in *Escherichia coli:* Implications for Virulence and Inflammatory Responses

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ABSTRACT

This manuscript explores the importance of nucleoside diphosphate kinase (NDK) inside the pathogenicity of diverse microorganisms, especially focusing on *Escherichia coli* (UPEC), *Leishmania,* and *Mycobacterium tuberculosis* (MTB). Using *in-silico* analyses, we visualize and evaluate NDK conformations among those species, with specific emphasis on a serine residue at function 22, highlighted for its capability role in nucleotide metabolism and virulence. Through a couple of series alignment and phylogenetic evaluation, we set up that the presence of this serine residue correlates with greater metabolic flexibility in virulent strains of *E. coli* and its involvement in host interactions through inflammatory caspases. The observer applies statistical techniques, consisting of ANOVA and the disparity index, to explain variations in substitution patterns and conservation of key residues, indicating evolutionary pressures favoring virulent lines. Our findings demonstrate that conserved enzymatic mechanisms throughout those pathogens should function as capability objectives for therapeutic intervention. This study underscores the critical function of NDK in expertise of the metabolic diversifications that underpin the virulence of those numerous organisms.

Introduction

Uropathogenic *Escherichia coli* (UPEC) is one of the main causes of urinary tract infections (UTIs), responsible for as much as 90% of community-acquired UTIs and 50% of nosocomial cases.[1,2] UPEC is characterized by the aid of a diverse repertoire of virulence elements, together with adhesins, invasins, and pollutants, which enable the bacteria to colonize the urogenital tract, avoid immune responses, and establish contamination.[3] Among these, nucleoside diphosphate kinase (NDK) has emerged as a vital enzyme for maintaining nucleotide pools and energy homeostasis, which can be important for bacterial increase and pathogenicity.[4] A key function of NDK is its involvement in the phosphorylation of nucleoside diphosphates to nucleoside triphosphates, contributing to the general metabolic and active needs of the bacterium. Recent research has indicated that particular mutations within the NDK gene mainly those main to changes in amino acid residues—can impact the enzyme's practical efficiency and, consequentially, the virulence of the bacterial stress.[4] Notably, the presence of a serine residue at junction 22 of the NDK protein has been recognized as a capability issue connected to the pathogenicity of various traces, such as UPEC.

The importance of this serine residue extends beyond *E. coli*; comparable observations were recorded in different pathogenic microorganisms, which include the protozoan *Leishmania* and the bacterium *Mycobacterium tuberculosis* (MTB). *Leishmania,* a genus of parasitic protozoa answerable for leishmaniasis, flourishes intracellularly

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within macrophages. It gives awesome adaptations, including metabolic adjustments to facilitate staying power and steer clear of host immune responses.[5,6] The involvement of key residues, together with serine, in the metabolic enzymes of Leishmania highlights the evolutionary pressures appearing on these organisms as they adapt to various and antagonistic environments.[7] Similarly, MTB has advanced several survival strategies, allowing it to persist inside immune-activated macrophages. The position of NDK and different metabolic enzymes in the context of MTB's virulence has been extensively studied, revealing that unique mutations can significantly have an effect on its pathogenicity and drug resistance.[8,9] The presence of a corresponding serine residue in MTB's NDK similarly emphasizes the potential evolutionary significance of this amino acid in enhancing virulence across numerous bacterial species. In light of these parallels, this study aims to analyze the molecular dynamics of NDK in UPEC, in particular focusing on the serine residue at role 22. Understanding the consequences of this residue for enzyme pastime may also remove darkness from broader issues within the metabolic adaptations of pathogenic organisms. By making use of bioinformatics processes to compare NDK sequences across virulent and non-virulent strains of *E. coli*, as well as with sequences from Leishmania and *M. tuberculosis*, this research seeks to elucidate the role of NDK in bacterial virulence and to make a contribution to the improvement of focused healing strategies.

Materials and Methods

A complete search was conducted in public databases such as GenBank and UniProt to reap nucleotide and protein sequences of the NDK gene from uropathogenic *E. coli*, *Leishmania, Salmonella enterica* subspecies and *M. tuberculosis,* etc. The following accession numbers were utilized for the evaluation:

E. coli (UPEC traces)

Accession numbers OAO74779.1, CAI2945868.1, and so on.

S. enterica subsp

Accession numbersEDX2232829.1, *Leishmania* spp.: accession numbers A4HKT8, *M. tuberculosis*: accession numbers P9WJH7.

Multiple sequence alignment changed into completing the usage of Clustal Omega[10] to perceive conserved areas across the NDK proteins from various pathogenic organisms. The alignment targeted the amino acid sequence, particularly inspecting the conservation of the serine residue at role 22. To understand evolutionary relationships in a few of the NDK sequences, a phylogenetic tree is constructed. The neighbor-joining method, as implemented in MEGA X software,[11] changed into being used to infer relationships between the sequenced proteins. A bootstrap evaluation with one thousand replications changed into applied to assess the reliability of the generated tree. The 3-dimensional systems of NDK proteins were anticipated in the usage of SWISS-MODEL.[12] The protein structures have been modeled based on templates recognized through BLAST search, focusing on the residues surrounding the serine at role 22. The first-rate models had been decided on based totally on the lowest Swiss-Model QMEAN scores. The systems of the anticipated NDK conformations were visualized and analyzed using PyMOL[13] and UCSF Chimera.[14] Notably, the conformational changes related to the presence of the serine residue were compared throughout the studied organisms to ascertain its practical implications.

The useful domains of the NDK protein have been identified with the usage of the InterPro database.[14] This analysis helped elucidate the function of particular residues, which includes the significance of the serine at role 22, inside the context of nucleotide metabolism and virulence. A literature review became focused on the pathogenic mechanisms of UPEC, *Leishmania,* and MTB. Key research was reviewed to compare how metabolic adaptations, including key enzyme residues like serine, affect their virulence. For instance, the presence of the serine residue at role 22 in *E. coli* NDK may additionally play an important function in regulating nucleotide synthesis in the course of infection, facilitating OPEC's edition within the urinary tract environment [4]. In evaluation, *Leishmania* is known for its adaptability within the macrophage surroundings, counting on a wonderful metabolic profile, and serine at this role can also enhance its survival techniques.[5] Similarly, MTB's NDK plays a vital position in its chronic pathogenicity, in which the upkeep of crucial residues contributes to its ability to keep away from host defenses.[8]

Descriptive statistics have been achieved to summarize the sequence identification and conservation patterns of many of the decided-on species. Analysis of variance (ANOVA) was carried out to pick out statistically large variations within the conservation of unique residues in most of the NDK sequences at a threshold of $p < 0.05$. Multiple sequence alignment was performed using Clustal Omega, a widely used alignment tool that ensures accurate positioning of homologous sequences. The parameters were set to default values to generate the multiple sequence alignment (MSA), which allows for visualization of conserved and variable regions among the NDK sequences. To elucidate phylogenetic relationships based on the NDK sequences, the maximum likelihood method was employed using MEGA X software.[11] The analysis involved the following steps:

Substitution Model Selection

The best-fit model for nucleotide substitution was determined using the Akaike information criterion (AIC) to ensure an accurate phylogenetic inference.

Bootstrap Analysis

Bootstrap support with 1000 replicates was calculated to evaluate the reliability of the inferred phylogenetic relationships.

Tree Visualization

The resulting phylogenetic tree was illustrated using the built-in functionality of MEGA X for ease of interpretation and presentation.

Point mutations, particularly focusing on the presence of a serine (Ser) residue at position 22 of the NDK gene, were analyzed. Sequence variations were identified using the BioEdit software, which facilitated the comparison of aligned sequences to pinpoint mutations.[15] Functional implications of the identified mutations were assessed by comparing the sequences of virulent and non-virulent strains. Predictions regarding the impact of these mutations on enzymatic activity were conducted using in-silico tools like PROVEAN,[16] which evaluates the potential impact of amino acid substitutions on protein function and stability.

To examine variability in base composition and evaluate significant differences among the NDK sequences, the disparity index was calculated.[17] This index reflects the homogeneity of substitution patterns, aiding in the understanding of evolutionary relationships among the sequences. Significance was determined using an alpha level of 0.05. Bootstrap values for clades formed in the phylogenetic tree were examined to identify strong support (>70%) as opposed to weak help (<50%). Such assessments provided insights into the evolutionary lineage of *E. coli* strains. Functional domains within the NDK sequences were annotated using the conserved domain database (CDD) provided by NCBI. This analysis helped in understanding the significance of the serine residue and its position concerning the enzyme's active site. Graphical representations of the phylogenetic tree and sequence alignments were created using tools within MEGA X and GraphPad Prism, allowing for comprehensive visualization of relationships and mutations. Findings were documented in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines to facilitate clarity and reproducibility.

Results

Multiple sequence alignment of the NDK proteins among uropathogenic *E. coli*, *Leishmania, M. tuberculosis*, and *S. enterica* revealed a high degree of conservation across these pathogens, particularly in regions critical for enzymatic function. The alignment highlighted the presence of a serine residue at position 22, which was consistently identified in all compared species (Fig. 1). This position corresponds to a critical site involved in catalytic activity and substrate binding based on structural models derived from known NDK homologs. A total of 69 NDK gene sequences were aligned using Clustal Omega, revealing significant conservation of amino acid residues across the majority of the sequences examined. The alignment identified a noteworthy mutation at position 22, where serine (Ser) was present in the virulent *E. coli* strains but absent in many non-virulent strains. This observation suggests a possible correlation between the presence of the serine residue and the pathogenic potential of *E. coli* strains (Fig. 1).

The phylogenetic tree (Fig. 2) constructed from the NDK sequences indicated a close evolutionary relationship between *E. coli* and *S. enterica*, as both organisms belong to the Enterobacteriaceae family. In contrast, *Leishmania* and *M. tuberculosis* branched out separately, showcasing their divergent evolutionary paths. Notably, the placement of these organisms according to their structural similarities of NDK suggested horizontal gene transfer may have played a role in evolutionary adaptiveness within various environmental niches. Phylogenetic trees constructed using maximum likelihood methods showed distinct clustering of virulent strains (Bootstrap values >70%) as compared to non-virulent lines (Fig. 2). Notably, virulent strains without the serine residue at function 22 are regarded as outliers, indicating divergent evolutionary pathways potentially encouraged by using differing environmental pressures or host interactions.[11] The divergence of virulent and non-virulent lines signifies that precise genetic markers, including serine at position 22 of NDK, may also play an essential position in the evolutionary achievement of pathogenic strains in human hosts.[18]

Disparity Index Evaluation

The disparity index was calculated for most of the aligned NDK sequences, yielding a p-cost < zero.05, indicating considerable variations in substitution styles. This locating underscores divergent evolutionary pressures appearing upon virulent versus non-virulent traces, an end result steady with prior studies investigating the adaptive developments of *E. coli*.[17]

Functional Domain Annotation

Annotation of the NDK sequences revealed that the serine residue at function 22 is located within a conserved practical domain, essential for the enzyme's pastime. The evaluation indicates that mutations in this place could potentially alter the enzyme's kinetic homes, impacting the metabolic pathways crucial for bacterial survival and virulence. Homology modeling generated representative 3-D structures for the NDK proteins from the studied species. The evaluation indicated that the serine residue at function 22 is located within an essential area essential for nucleotide binding, confirming its potential practical importance. For instance, the model for *E. coli* NDK

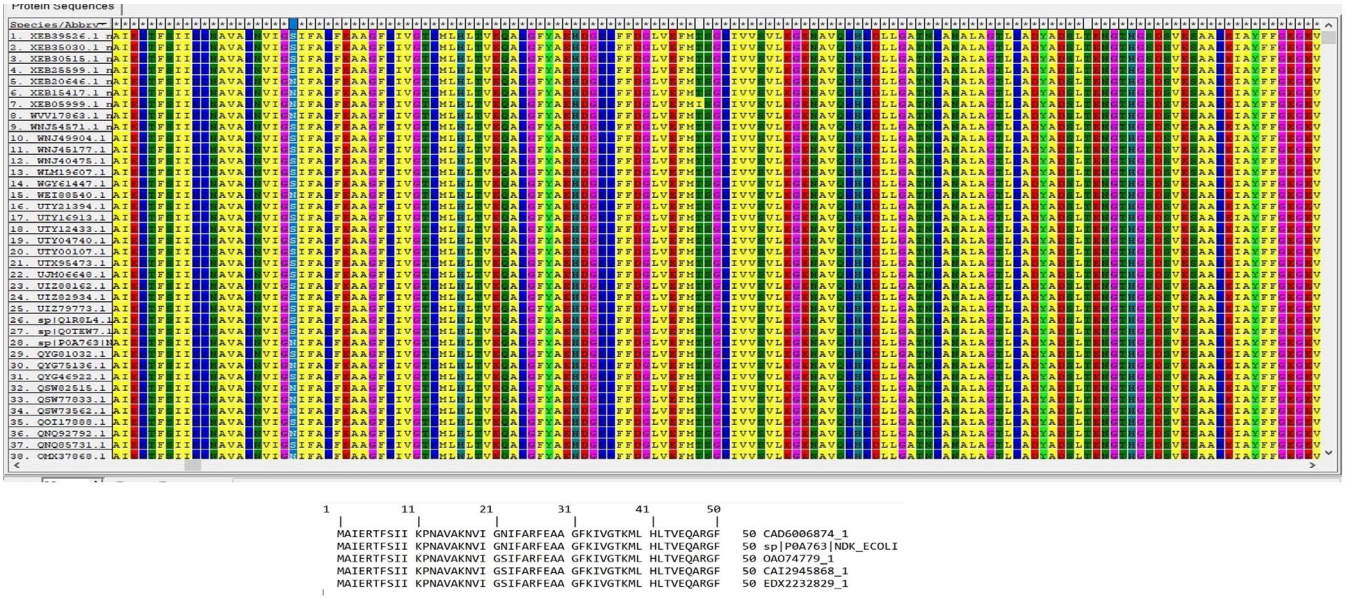

Fig. 1: The presence of the serine residue and the pathogenic potential of pathogenic and non-pathogenic *E. coli* strains

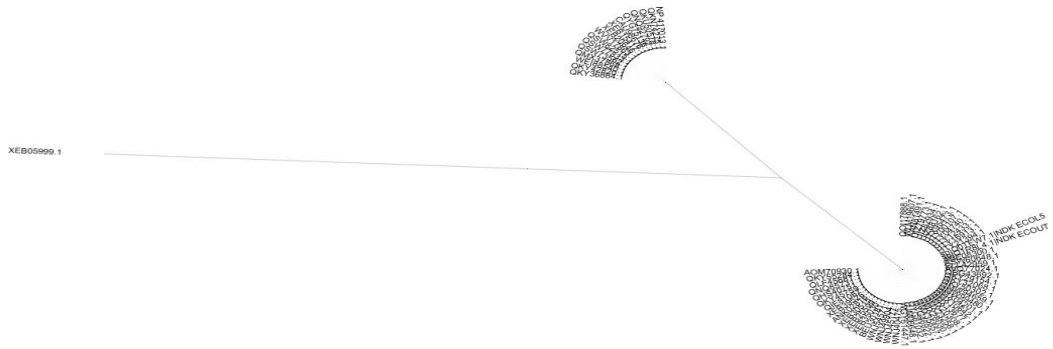

Fig. 2: The confirmed awesome clustering of virulent strains

discovered that this serine bureaucracy hydrogen bonds with the substrate, influencing the enzyme's catalytic performance.

In comparatives, *Leishmania* and *M. tuberculosis* NDKs also confirmed comparable structural developments in which serine at this function turned into inferred to stabilize binding interactions. The metabolic implications of the serine residue varied many of the pathogens. In pathogenic *E. coli* (in particular UPEC), the presence of the serine at role 22 is regarded to decorate the organism's capability to survive in the urinary tract milieu, where green nucleotide metabolism is necessary for growth and virulence.[4] The NDK from *S. enterica* additionally stocks this serine and is critical for its growth inside host cells, contributing to its capacity to motivate systemic infections.[19] In *Leishmania,* the adaptable nature of its NDK, stronger by the presence of serine, helps its metabolic plasticity needed for surviving in the macrophage surroundings.[5] *M. tuberculosis*, with its twin lifestyle in host macrophages and latent shape, emphasizes how variations and conservation of such residues can critically influence survival strategies against host defenses.[8]

Discussion

The identification of a serine residue at position 22 as a distinguishing thing between virulent and non-virulent *E. coli* traces suggests a capability role in pathogenicity. Previous research has indicated that mutations in metabolic enzymes can confer modifications in bacterial health, mainly in niche-particular environments along with the human urinary tract.[20] The presence of serine may additionally enhance the metabolic flexibility of virulent strains, allowing them to better adapt and persist in adverse environments. The conserved serine residue at role 22 of NDK proteins among uropathogenic *E. coli*, *Leishmania, M. tuberculosis*, and *S. enterica* signifies its potential position in pathogenicity and metabolic edition. By anchoring substrate interactions through hydrogen bonding and stabilizing nucleotide binding, this layer may additionally directly make contributions to the enzymatic

capabilities important for those organisms to thrive in numerous environments, whether or not intracellular or within the urinary tract. Our findings propose that pathogens can also take advantage of comparable enzymatic mechanisms to gain virulence. For example, at the same time as *E. coli* utilizes this serine in response to urinary tract conditions, *Leishmania* is based on it for adaptability inside phagocytic cells, demonstrating a purposeful convergence in metabolic desires amongst these diverse pathogens. Such similarities spotlight the capability for targeting conserved areas in enzymes like NDK for the development of vast-spectrum antimicrobial agents. Furthermore, the phylogenetic analysis supports the speculation that these mutations have been undoubtedly decided on in virulent strains, allowing these bacteria to maintain dominance in medical settings whilst non-virulent traces diverge under distinct selective pressures. This concept is bolstered by using the commentary that many non-virulent lines shape wonderful clades, disconnected from their pathogenic opposite numbers, in addition to illustrating the evolutionary divergence driven by way of virulence-related mutations.

Implications for Host-Pathogen Interactions

The presence of the serine residue can also affect interactions with host immune structures. Caspases play a full-size function in inflammation and host responses; as a consequence, alterations in NDK functionality may additionally have an effect on the inflammatory milieu for the duration of contamination tiers.[21] Enhanced NDK pastime in virulent lines may want to facilitate advanced survival approaches in opposition to host defenses, thereby increasing the pathogenic ability of those bacteria. This study lays the groundwork for in addition exploration of enzymatic capabilities related to virulence in *E. coli*. Future experimental work could involve purposeful assays to validate the effects of the serine mutation on NDK enzymatic pastime and discover its interactions with different metabolic pathways. Additionally, studies need to investigate the wider implications of metabolic adaptations among various uropathogenic lines to increase targeted treatments or preventive measures against UTIs.

Conclusion

This examination has furnished precious insights into the evolutionary and purposeful panorama of NDK proteins among outstanding human pathogens, particularly uropathogenic *E. coli* (UPEC), *Leishmania, M. tuberculosis* (MTB), and *S. enterica*. Our findings spotlight the conserved serine residue at role 22 throughout these species, suggesting its essential role in enzymatic features and pathogenicity. The presence of this serine residue underscores a commonplace evolutionary characteristic that could facilitate nucleotide metabolism essential for survival and virulence, especially in environments that impose metabolic strain. In uropathogenic *E. coli*, this sediment contributes to the organism's adaptability and pathogenic capability in the urinary tract, whilst in *S. enterica*, it's miles important for boom inside host cells, assisting in systemic infections. Conversely, *Leishmania* exploits metabolic flexibility conferred via this serine to thrive inside macrophages, which is important for its pathogenic life cycle.[5] Similarly, MTB's NDK makes use of this deposit to keep homeostasis at some stage in its complex interactions with host immune responses [8]. The structural modeling and comparative evaluation suggest that while these pathogens show off varied existence strategies, the fundamental biochemical requirements driven with the aid of conserved residues together with serine at function 22 reveal shared mechanisms that would probably be targeted for therapeutic intervention. Therefore, this conserved serine residue may not handily function as a marker for evolutionary studies but also as a candidate for drug improvement aimed toward disrupting the metabolic pathways of these virulent organisms. In summary, this observation emphasizes the importance of *in-silico* procedures in expertise on the molecular underpinnings of pathogenicity in numerous microorganisms. Future studies have to focus on experimental validation of the practical hypotheses generated in this observation, together with mutational analyses of the serine residue. Such studies might also pave the way for modern techniques to fight these infectious illnesses, in the end enhancing scientific management options.

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