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Original Research

Klebsiella pneumonia: Epidemiology, Causes, Effects, Pathogenicity and Its Secondary Metabolites

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Abstract:

Klebsiella pneumoniae, an opportunistic pathogen, can infect humans by colonising mucosal surfaces and then spreading to other parts of the body. The germs Klebsiella are present in water, soil, and animals, and they can colonise healthcare facilities and medical equipment. This microbe is also responsible for a large number of community-acquired diseases around the world. These infections can spread to other parts of the body and cause a lot of problems, like death and illness. These infections may be associated with hypervirulent Klebsiella strains. The cell wall, lipopolysaccharide, fimbriae, and siderophores are the four main parts of this pathogenic bacterium. As a secondary metabolite, siderophores enable bacteria to take iron from their environment and transfer it to their internal compartment. Colonisation of a particular location by Klebsiella pneumoniae can occur for many different reasons. The local healthcare practices, antibiotic usage and misuse, infection control measures, nutrition, gender, age, and age all play a role in the risk of infection. Mechanisms of bacterial survival, development, and virulent infection are all part of the pathophysiology. Put another way, K. pneumoniae's pathophysiology is closely related to its CPS and LPS abilities to avoid the host's immune system, fimbriae's efficiency in attaching and colonising, and OMPs' ability to collect nutrients from its environment. But, iron-binding siderophores (described in detail below) play a significant role in the pathophysiology of Klebsiella pneumoniae by facilitating iron intake.

Keywords: *Klebsiella pneumonia*, pathogenesis; epidemiology, Secondary metabolites.

Introduction:

The Gram-negative bacterium Klebsiella pneumoniae, or K. pneumoniae, is an opportunistic pathogen that can infect humans and cause a wide range of illnesses. Klebsiella pneumoniae used to be linked to bacteremia, pneumonia, and UTIs among those who were often hospitalised or had compromised immune systems. In addition to being resistant to other antibiotics, K. pneumoniae

isolates from the carbapenem-resistant Enterobacteriaceae (CRE) family are ineffective against carbapenems, which are commonly used in clinical practice. The isolates in question have been identified as a "critical concern" by the World Health Organisation (WHO) [1], highlighting the pressing need for more antibiotic studies to address this grave threat to human health. Klebsiella pneumoniae is the leading pathogen responsible for nosocomial pneumonia, and it is one of the rare Gram-negative rods that can cause primary pneumonia. Nobody wants to get Klebsiella pneumoniae (cKP) in their hospital, especially if they're old or have a compromised immune system [2]. A novel strain of Klebsiella pneumoniae known as hypervirulent K. pneumoniae (hvKp) has emerged in recent decades and can infect both healthy individuals and those with compromised immune systems. When compared to cKP, the hypervirulent strain can infect healthy people and is frequently linked to high rates of pathogenicity and fatality. Liver abscesses are the most common symptom of hvKp infection in healthy individuals, however the virus can also cause meningitis, endophthalmitis, pneumonia, and other infections. In an immunocompetent host, hvKp is able to spread metastatically from the infection site, setting it apart from other Enterobacteriaceae members [3]. The bulk of hvKp strains seem to be antibiotic-resistant. However, it seems like there is some mixing going on between the hvKp and antibiotic-resistant cKP phenotypes. Previous studies have demonstrated that certain hvKp bacteria have the ability to produce carbapenemases and extended-spectrum β-lactamases (ESBLs), which enable them to evolve into antibiotic-resistant strains. The pathogenic components of hvKp include lipopolysaccharides (LPS), siderophores, capsules, and fimbriae [8]. Siderophores and other small iron-binding metabolites are particularly noteworthy. The bioavailability of iron is typically lower than the micromolar concentration required for bacterial development, despite the fact that bacteria cannot survive without iron. Free iron (Fe^{3+}) is limited under normal physiological settings due to iron binding to transferrin and heme when an infection is present. Bacterial iron absorption in vivo is often dependent on an iron acquisition route that is siderophore-dependent. Bacteria produce and secrete these chemicals, which bind to environmental iron ions and transport them into cells [5]. The importance of siderophores in bacterial pathogenesis and survival is typically attributed to this reason. The iron siderophore complexes are delivered to the periplasm, where they mix with binding proteins, and then are detected by specific receptors on the outer membrane. From there, they are transported to the inner membrane. Upon entering the cytoplasm, ferric iron is converted from ferrous iron by an ATP-binding cassette (ABC) transporter, which the pathogen utilises [6]. Prior research has shown that, in comparison to cKP, the hypervirulent strain produces six to ten times the amount of siderophore, including enterobactin (Ent), salmochelin (Iro), yersiniabactin (Ybt), and aerobactin (Iuc). These four siderophores improve the efficiency of bacterial growth. But human neutrophils and epithelial cells secrete lipocalin-2 (Lcn2), which binds to iron-loaded Ent and inhibits bacterial uptake, limiting iron absorption via Ent. Not all Enterobacteria are harmful; some of the less toxic ones secrete the main siderophore, Ent. When siderocalin is removed from the modified Ent, the resulting compound is known as salmochelin. Aside from Klebsiella, other bacteria that utilise it include E. coli and Salmonella. Having said that, none of the other three siderophores bind to Lcn2. Salmochelin is an alternative Ent protein that pathogenic strains have evolved to collect iron during infection and compensate for this inhibition. Harmful Gram-negative bacterial strains can evade detection by the host's innate immune system because salmochelin can evade capture by Lcn2. In a mouse sepsis model, this bacterial growth encouraged by the host organism has been linked to increased virulence. Aerobactin (Iuc), on the other hand, has a checkered past when it comes to its association with pathogenicity. Various studies in murine models, ascites fluid from humans, and blood have shown that it plays a key role in altered iron uptake, bacterial proliferation, and toxicities. It seems that Iuc is the most significant factor

impacting virulence in both laboratory and living organism environments, even in strains that possess all four siderophore-encoding loci [7]. It has additional potential as a biomarker for the detection of highly pathogenic isolates. The paper summarises the four bacterial siderophores—biosynthesis, export, import, and genetic control—and dives into the pathophysiology of Klebsiella pneumoniae.

Klebsiella pneumoniae: sources, symptoms, and consequences:

The common opportunistic Klebsiella pneumoniae can cause severe illness and death in those whose immune systems are already compromised or who have had prior infections. K. pneumoniae is a highly invasive and hypervirulent bacteria that can cause a variety of community-acquired infections, including meningitis, endophthalmitis, severe pneumonia, meningitis, and pyogenic liver abscess. Before a hospital-acquired infection occurs, the gastrointestinal (GI) tract is often colonised by Klebsiella pneumoniae. Additionally, colonisation has the potential to spread to many organs and systems, such as the bloodstream, lungs, and urinary system. Klebsiella pneumoniae is infectious in and of itself, but it also forms biofilms on a variety of medical equipment, including endotracheal tubes and catheters, increasing the risk of infection for patients having catheterization [7]. Additionally, K. pneumoniae nosocomial infections can persist for a long time due to two main reasons: first, the bacteria can evade the immune system in living things by forming biofilms. Second, they can produce enzymes that make antibiotics ineffective, such as carbapenemases or extended-spectrum β-lactamases, which can make the bacteria resistant to antibiotics. Antibiotic treatment has become very challenging, if not impossible, due to the evolution of enzymes that resist antibiotics. After entering the body through the respiratory tract, Klebsiella pneumoniae can cause a severe case of pneumonia in humans by infecting the lungs. The ability of Klebsiella pneumoniae to evade the host immune system, particularly by rendering immune cells less effective at phagocytosis, is a key factor in the development of a detectable infection. Significant study has been conducted on the pathogenic components of Klebsiella pneumoniae. This process includes the production of fimbriae, outer membrane proteins (OMPs), capsular polysaccharides (CPSs), lipopolysaccharides (LPSs), and iron-binding siderophores. The acid polysaccharide carbohydrate-polysaccharide complex (CPS) containing three to six sugar repeating units is an important component of Klebsiella pneumonia's pathogenicity. Through the cps gene cluster, it is controlled by the Wzy-dependent polymerization process [8]. The intracellular transport of CPS is followed by its export to the cell surface following Wzy-dependent polymerization. Glycosyltransferases catalyse the first step in this process, which is to construct units of single sugar repeats. Once pathogens pass the epithelial barrier, they become susceptible to phagocytosis by dendritic cells, neutrophils, and macrophages. However, the thick capsule of K. pneumoniae prevents immune cells from adhering to or internalising the bacteria. Hypervirulent K. pneumoniae actually has a K1-CPS that significantly limits bacterial-macrophage interactions compared to non-hypervirulent strains. By inhibiting the release of IL-8 by respiratory route lining cells, CPS amplifies its anti-inflammatory actions. The Toll-like receptors (TLRs) expressed by these cells are blocked, allowing the release of IL-8 to proceed [9]. These receptors detect chemicals on cell surfaces that contain pathogens. CPS has the ability to bind to Toll-like receptors 2 and 4, which in turn inhibit the transmission of signals downstream by pulmonary epithelial cells [19]. In response to pathogen detection, airway epithelial cells release a synergistic blend of antimicrobial polypeptides. These antimicrobial chemicals cannot reach the surface of K. pneumoniae because of the surface-attached CPSs, but they are captured in transit by the free-floating CPSs released by the bacteria. Epithelial cells are unable to secrete antimicrobial compounds because CPS blocks TLR-mediated responses. The chemopreventive signalling pathway (CPS) from Klebsiella pneumoniae can also impede DC maturation, leading to a reduction in natural killer cell number and migration to the site of infection [10]. Another role of CPSs in immune response evasion is their ability to block the development of complement system components, which in turn prevent the bacterial outer membrane from being breached by membrane attack complex pores.

Along with CPS and LPS, K. pneumoniae also contains thin appendages on its surface membranes known as fimbriae. Experiments have confirmed four different types of fimbriae: type 1, type 3, Kpc, and KPF-28. Fibroa, which are thread-like extensions on the surface of bacteria's outer

membrane, are thin, stiff, and sticky. Bacteria are able to adhere to mannose-rich substances outside of cells or extracellular matrix via these extensions, which also extend outside the capsule. Therefore, fimbriae play a crucial role in bacterial adhesion to and infection transmission within internal tissues. Type 3 fimbriae enable Klebsiella pneumoniae to cling to the epithelial cells located in the kidneys and lungs, whereas type 1 fimbriae are necessary for infection of the urinary system. In contrast, Klebsiella pneumoniae's type 3 and kpc fimbriae are major players in biofilm development [11]. One of the numerous bacteria whose capacity to form biofilms is believed to be a crucial component of their pathogenicity is Klebsiella pneumoniae. Actually, biofilms are the root cause of 65–80% of bacterial illnesses. Bacteria in biofilms have a major advantage because they are more resistant to exogenous stressors, antimicrobial treatments, human immunity, and other similar threats. The attachment of these microscopic pili structures to abiotic surfaces (such as urinary catheters) and extracellular matrix proteins (such as type IV and V collagens) demonstrates their remarkable function in biofilm development [12]. Experimental evidence suggests that KPF-28 fimbriae contribute to bacterial colonisation of the intestines because they allow Klebsiella pneumoniae to cling to human colon cancer cell lines. Last but not least, the aforementioned factors are not the only ones that contribute to Klebsiella pneumoniae's pathogenicity. The remaining piece of the virulence jigsaw puzzle that all the other virulent components have abandoned are outer membrane proteins (OMPs). K. pneumoniae's OmpA is a key outer membrane protein that can dampen the inflammatory response that airway epithelial cells start. Therefore, this inhibitory role of OmpA is both independent of and additive to CPS, meaning that CPS alone is not enough to commence full regulation of the epithelial-inflammatory response. When expressed in host cells, OmpA may withstand the cytotoxic effects of antimicrobial chemicals and can prevent macrophages in alveolar sacs from phagocytosing. Outer membrane proteins (OMPs) are another significant class of OMPs. In addition to facilitating the entry of nutrients, carbohydrates, and hydrophilic molecules essential for growth, these porins aid bacteria in evading phagocytosis. An efflux pump from a distinct class of surface proteins is the AcrAB pump in Klebsiella pneumoniae. These vital organelles allow bacteria to expel harmful substances such as antibiotics, antimicrobial peptides, and more.

Health promotion:

Men in their middle years and beyond are more prone to suffer from debilitating diseases than women of the same age. Respiratory host defences are believed to be weakened in people with diabetes, alcoholism, cancer, liver illness, chronic obstructive pulmonary disease (COPD), renal failure, glucocorticoid medication, and some occupational exposures (e.g., papermill workers) [13]. One type of illness that can spread from person to person in a healthcare setting is known as a nosocomial infection.

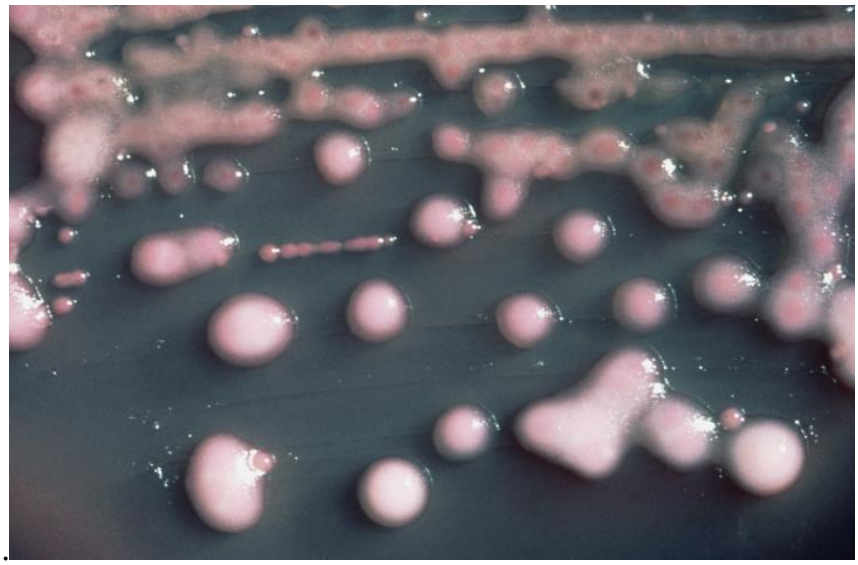

Figure 1. The tiny rod-shaped, facultatively anaerobic Klebsiella pneumoniae bacteria grew colonially on a MacConkey agar culture plate. The bacteria are Gram-negative. Nosocomial infections, which affect the urinary and pulmonary systems, are frequently caused by K. pneumoniae bacteria, which are prevalent in the human gastrointestinal tract.

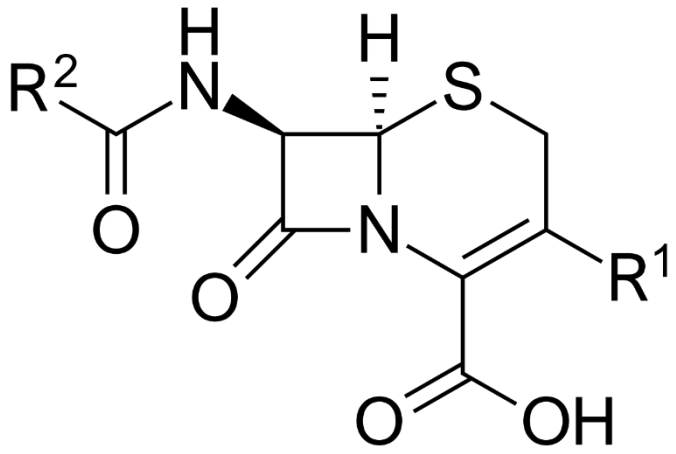

Figure 2. Cephalosporin (core structure)

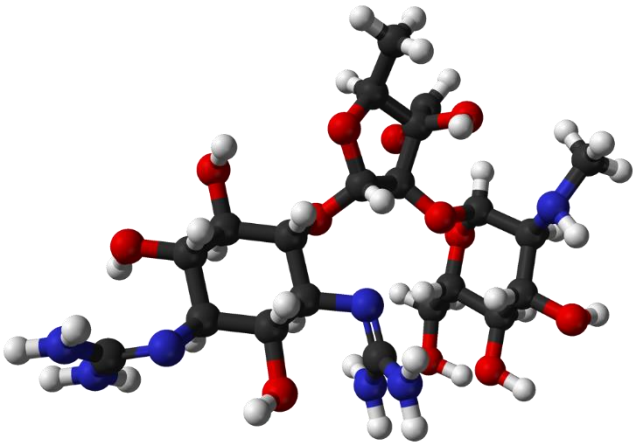

Figure 3. Streptomycin(Aminoglycoside)

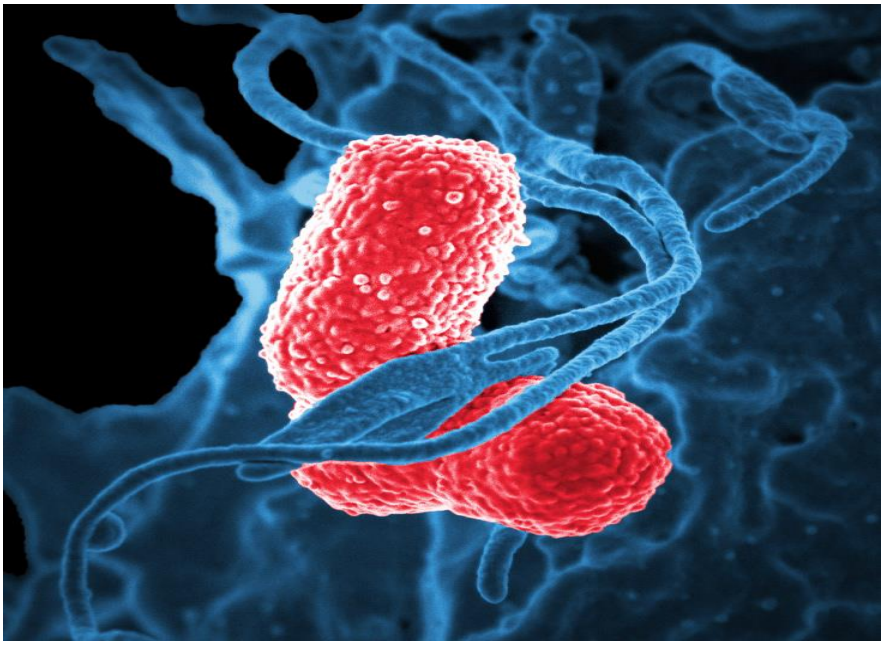

Figure 4. Multidrug-resistant Klebsiella pneumoniae

The urinary tract, the lower biliary tract, and surgical incision sites are among the many places Klebsiella can cause infections. Pneumonia is no exception. The clinical conditions encompass a wide spectrum and include conditions such as pneumonia, thrombophlebitis, UTI, cholecystitis,

diarrhoea, UTI, wound infection, osteomyelitis, meningitis, bacteremia, and sepsis. Contamination of invasive medical devices poses a risk to patients. This is especially true for patients with devices used in neonatal wards, respiratory support systems, and urine catheters [14]. Another risk factor for nosocomial infection with Klebsiella bacteria is the use of antibiotics. Bacterial infection in the bloodstream can cause sepsis and septic shock.

Scientists at King's College, London have shown that ankylosing spondylitis is caused by chemical mimicry between two molecules on the surface of Klebsiella and HLA-B27. When it comes to UTIs in the elderly, Klebsiella is second only to Escherichia coli. In addition to opportunistic infections, it can cause chronic lung disease, intestinal pathogenicity, rhinoscleroma, and atrophy of the nasal mucosa.[reference required] There are new strains of Klebsiella pneumoniae that are resistant to antibiotics.

Medical Care:

A person's health status, medical history, disease severity, antibiotic susceptibility tests, and other factors determine the antibiotic choice for treating Klebsiella pneumoniae [14]. Antibiotics such aminoglycosides, pipercillin tazobactam, and cephalosporins are among the options. Klebsiella is resistant to ampicillin because it has beta-lactamase. There is a high prevalence of isolates that have developed resistance to carbenicillin, amoxicillin, and ceftazidime, as well as an extended-spectrum beta-lactamase. The bacteria can still be killed by aminoglycosides and certain cephalosporins. Clavulanic acid has been found to block the beta-lactamase enzyme to different degrees. A resurgence of colistin has been prompted by infections in the intensive care unit caused by gram-negative bacteria that are resistant to many drugs. But there have been reports of K. pneumoniae strains in intensive care units that are resistant to colistin [15]. It wasn't until 2009 that researchers in Pakistan and India found Klebsiella pneumoniae bacteria with the gene NDM-1, which confers resistance to carbapenem, an intravenous antibiotic. People with diabetes mellitus (DM) have developed liver abscesses due to aberrant toxicity caused by Klebsiella; third generation cephalosporins are used for treatment.

Klebsiella pneumonia with hypervirulence:

The hypervirulent (hvKp) strain of Klebsiella pneumoniae is a relatively new variation of the disease that is far deadlier than the classic (cKp) strain. Although cKp is an opportunistic pathogen that typically infects immunocompromised patients, hvKp poses a greater clinical issue because to its ability to infect almost every part of the body and cause sickness in healthy individuals as well. Several conjugative elements and a big virulence plasmid include the genes responsible for this pathotype. Among other things, these recently discovered strains were said to overproduce siderophores and capsule components in order to get iron. Despite early research suggesting that hvKp is amenable to antibiotic treatment, new evidence suggests that these strains can acquire resistance plasmids and develop multi-drug resistance [28]. Its high death rate is associated with its Asian ancestry. It frequently causes meningitis, endophthalmitis, pneumonia, necrotizing fasciitis [16], and nonhepatic abscesses after spreading to the central nervous system and the eye. The hypermucoviscous phenotype is a visible characteristic of these strains that can be further confirmed by a string test. There are currently no international recommendations, so further investigations and treatments are done on an individual case basis.

Extracellular Molecules:

All of an organism's biological reactions put together make up its metabolism. Typically, metabolites are tiny molecules that serve as metabolic intermediates or end products. The term "secondary" was first used by A. Kossel in 1891 to describe metabolites that are not essential to an organism's survival, as opposed to the primary metabolites that are present in all cells that may divide. Although they are byproducts of primary metabolism, secondary metabolites are not structural components of the living thing [17]. In contrast to primary metabolites, its absence does not instantly kill an organism, but it significantly

reduces the organism's chances of survival. Ecologically disadvantaged species within a phylogenetic group are the ones that have it and are able to synthesise it.

Since many of the intermediates in primary metabolism overlap with the intermediates of secondary metabolites, the distinction between primary and secondary metabolites is unclear. Despite their status as a primary metabolite byproduct, amino acids are also unquestionably a secondary metabolite. While it's true that sterols are essential components of numerous cellular structures, this is not necessarily the case. The shared metabolic pathway between primary and secondary metabolism is indicated by the mosaic character of an intermediate.

To prevent the primary metabolic process from becoming inactive due to an excess of carbon and nitrogen, secondary metabolites provide a buffer zone. Metabolic breakdown of secondary metabolites allows the stored carbon and nitrogen to return to primary metabolites upon demand. The processes of primary and secondary metabolism are constantly changing and intricately balanced, depending on factors such as the cell's or body's [18] internal and external environments, as well as its own growth, tissue differentiation, and development.

Metabolites produced by microbes and their characteristics:

• The idea and method of synthesising natural fermentation products can be effectively used to increase its impact on the medical, agricultural, food, and environmental sectors.

• The metabolite can be used as a building block to create a desired product, which can then be further modified through chemical or biological processes.
• The development of new compounds can be sped up by creating analogues or templates that use secondary metabolites as lead molecules.

Uses for Secondary Metabolites Produced by Microbes:

Many of the specialised metabolites produced by microbes have shown to have substantial impacts on human nutrition, health, and the economy, and they frequently have peculiar structures. Secondary metabolism, which occurs independently of the primary development phase of microbes, typically produces these chemicals, which have a low molecular mass. Chemicals with hormonal activity or specific effects on the metabolism of fats or carbohydrates are also included, as are antibiotics, pigments, poisons, enzyme inhibitors, immunomodulators, and effectors of ecological competition or symbiosis. Certain compounds have proven themselves to be effective against various microorganisms, viruses, antioxidants, tumours, narrowing or widening of blood vessels [19], and other medical conditions. Still others serve as insecticides, growth regulators, or colourants for various living things. The majority of the medications that have been approved by the FDA for use in human medicine come from microbes. Nutritional supplies, growth conditions, feedback regulation, enzyme induction or inactivation, and specialised metabolite synthesis can be fine-tuned. Certain molecules with modest molecular mass, as well as transfer RNA, σ factors, and gene products produced during post-exponential development, frequently impact their regulation. Recent studies have shown that clustered genes on chromosomal DNA, not plasmidic DNA, are the primary loci encoding specialised metabolite synthesis. Enzymology, control, and differentiation scholars still need a complete understanding of the associated pathways, which presents a new theoretical frontier.

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Results Interpretation in the Biological Domain:

Transitioning from changes in metabolite concentration in bodily fluids to interpretation in organ biochemistry and (molecular) physiology is still an area where a lot of information is lacking. The limited amount of data that is now available is often specialised to a single species, organ, or bodily fluid, and it is not easy to transfer this data to another. That isn't being considered by software tools like route or enrichment analysis [22]. If it is discovered that metabolite X from a different pathway is lowered, what does it actually mean? A drop in metabolite X concentration may result from either an increase in the activity of enzymes further down the pathway or a decrease in the activity of the enzyme itself. In order to maintain cellular homeostasis, enzyme activity can be modulated by their specific products through steric inhibition, feedback inhibition, or activation. This approach sidesteps major metabolic shifts that could harm the cell. Metabolites are involved in numerous pathways and are either produced by or used as a substrate by a wide variety of enzymes and metabolic processes. As a result, identifying the exact route or enzyme responsible for a changed metabolite can be quite challenging. However, the data on the pathways may already provide the right response, or at least a clue, to a biological query. By associating changes in metabolite abundances with certain pathways, one can obtain mechanistic details about the process being studied. Metabolic profiling data can be enhanced with other genomic, proteomic, clinical, and environmental information to help find biomarkers that might not have been found with targeted research alone.

One benefit of metabolome profiles is their ability to detect changes on a worldwide scale as well as undiscovered chemicals (shotgun) (shotgun and targeted). Because many metabolites come from several sources, confirmation requires targeted approaches, such as isotope-labeled MFA or enzyme knockdown. Metabolomics researchers are always developing new bioinformatics tools to help with things like analysing profiling data and answering other crucial problems in the area. Comprehensive metabolomic data processing, visualisation, and interpretation, including complex statistical computations, are made possible by MetaboAnalyst (www.metaboanalyst.ca). At the system level, metabolic profile data can be seen and understood biologically with the help of metabolic pathway enrichment analysis (MPEA). Using a ranked query compound list, the tool determines if metabolites that are part of certain preset pathways are [23] at the beginning or end of the list. One method for analysing pathway over-representation and enrichment using expression and metabolite data is IMPaLA, or Integrated Molecular Pathway Level Analysis. This demonstrates the significance of metabolomics; yet, many of these programmes receive financing for a limited time before being discontinued or becoming obsolete due to permanent changes in file formats and accompanying software. On top of that, the majority of programmes have their own unique requirements for raw or input data, which are often not compatible with one another. In order to identify unique and specific metabolic traits that are indicative of particular clinical disorders,

illnesses, or cancers, biomarker research is fueled by the use of new technology, protocols, and software tools [24]. Incredibly, the moment of clinical breakthrough has not yet arrived. However, there have been reports of metabolomic important features that are predictive of disorders such as schizophrenia, depression, diabetes, liver, ovarian, and breast malignancies, and cardiovascular and coronary artery disease. There is enormous and ever-changing variance in metabolic level across individuals, tissues, and time points. In contrast to the highly variable metabolites, the states of the genome, epigenome, transcriptome, and proteome are far more stable. The goal of research into biomarkers is to identify indicators of cancer at an early stage so that patients can receive the most effective treatment and have the best chance of survival. No novel biomarkers have been approved in recent years. The present approach to illness biomarker discovery is hindered by metabolite variations, which are both high and dynamic [25-29]. We should likely look for classes of metabolites or pathways that are differentially regulated for more reliable biomarkers in the future, since every disease alters not just one metabolite but entire metabolic networks. An integrative strategy that considers several subdisciplines of omics is the most effective way to achieve this. Revealing, assessing, and tracking molecular patterns—which reflect disease-perturbed networks—will, therefore, require reliable multi-data analyses.

Conclusion:

The Gram-negative bacterium Klebsiella pneumoniae is on the rise and poses a major threat to human health, causing organ failure and potentially fatal infections. At present, doctors have distinct challenges when dealing with classical K. pneumoniae (cKp) and hypervirulent K. pneumoniae (hvKp), two pathotypes of K. pneumoniae. While both pathotypes are prevalent globally, the Asian Pacific Rim countries have had a consistent increase in hvKp infections over the last 30 years. On the other hand, cKp has long been the most common offending agent in Western nations, although hvKp infections are starting to get some attention elsewhere. The majority of virulence factors—capsules, siderophores, lipopolysaccharides, fimbriae, proteins in the outer membrane, and the type 6 secretion system—are required for survival and pathogenicity. Microbes rely on siderophores, which are iron chelators with a high affinity and a low molecular weight, to proliferate and cause injury. During infection, Klebsiella pneumoniae secretes a unique blend of siderophores that influence host survival, systemic dissemination, and tissue localization. Hypervirulent K. pneumoniae clones, which cause severe community-related diseases like pneumonia and liver abscess, often contain gene clusters that encode the synthesis of the siderophores salmochelin (iro) and aerobactin (iuc), which are associated with invasive sickness. But it's just as worrisome when people report iuc in MDR strains while hospitalised.

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