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The Metabolic Flexibility of Staphylococcus Aureus: Linking Nutrient Adaptation to Persistence and Pathogenicity

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Annotation: Staphylococcus aureus is a human commensal that can provoke mild localized infections, as well as disperse to cause a range of severe diseases, including endocarditis, pneumonia, and sepsis. Its ability to infect such a diverse array of host-derived microenvironments implicates a remarkable metabolic flexibility that allows it to optimize growth in the face of nonpreferred carbon sources, potential nutrient starvation, and persisting host inflammation. In addition to broad nutrient utilization, adaptive rewiring of central metabolic pathways contributes to S. aureus survival and persistence. The metabolic determinants of persistence apparently connect with full pathogenicity, suggesting that metabolic adaptation also supports virulence during infection .

Metabolic cross talk between host and pathogen follows three major steps: sensing, adapting, and competing. One feature of many host–pathogen interactions is the first step in that the two parties typically regulate gene expression and enzyme or transporter activity in response to changes in nutrient

availability. Consequently, growth and virulence follow the available nutrient supply. For S. aureus, this means that central metabolism fuels the generation of precursors for protein biogenesis, energy conservation, and therefore growth. Discrete metabolic pathways also produce activated cofactors such as NAD^+, NADP^+, and FAD^++, whose levels orchestrate carbon flux through central metabolic pathways. Since a high degree of cellular fitness is required to maintain pathogenesis, pathogens must adjust their central metabolic pathways to suit their carbon source.

1. Introduction

Staphylococcus aureus colonizes a variety of niches and causes a spectrum of suppurative infections in humans and animals. It can quickly alter its metabolism in response to challenges and environmental changes, which contributes to its ability to persist and circulate between environments. Studying staphylococcal behavior at the metabolite level sheds light on mechanisms that allow survival under diverse conditions and enhance persistence in various environmental or clinical settings [1].

S. aureus has the capacity to reside in metabolically inactive forms for extended periods, which allows it to remain dormant before it ultimately resumes growth and leads to relapsing infections. This remarkable metabolic plasticity, which enables the exploitation of a variety of alternative nutrient sources, plays a crucial role in its ability to persist and cause recurrent disease episodes. In addition to this, S. aureus employs a range of protein toxins along with various immune-modulating factors to effectively evade the host immune responses, which is essential for establishing and maintaining an infection. Elucidating the complex mechanisms that regulate the process of switching between metabolically active and inactive states, as well as the means to sustain survival during periods of dormancy, has therefore garnered considerable interest among researchers in the field. Understanding these intricate mechanisms is critical for devising more effective therapeutic interventions against infections caused by S. aureus. [2][3]

2. Overview of Staphylococcus aureus

Staphylococcus aureus is an opportunistic pathogen routinely present in the skin and mucosa of healthy individuals. However, it can also cause infections ranging from superficial skin damage to severe invasive diseases. An important trait in the organism's survival permits it to infect such diverse tissue sites with different niches. These diverse tissue sites require specific carbon metabolic profiles. For example, when S. aureus infects abscesses, the bacteria must rely on glycolysis and fermentation. The metabolic flexibility of S. aureus allows it to meet its energy needs by using different available nutrients. This results in changes in the metabolic profile of the bacteria, which in turn changes the expression of virulence determinants that help the bacteria survive and counter the host immune response. S. aureus hides itself in adverse niches outlined by

the host immune response by switching its metabolism according to the available nutrients and also by hijacking the host immune response.

The persistent nature of S. aureus in the infected host also leads to antibiotic tolerance. The extensive use of antibiotics has contributed to the emergence of antibiotic-resistant bacteria, which are responsible for an alarming number of deaths worldwide. Therefore, a clear understanding of the metabolic flexibility of S. aureus, which enables the bacteria to survive antibiotic exposure, would help in developing strategies to counter antibiotic tolerance and hence aid in the treatment of chronic S. aureus infections. It is already known that S. aureus can adapt to available nutrients and persist in the host despite an active immune response. This stress adaptability is enabled by the metabolic flexibility of the bacteria. Moreover, metabolic pathways provide important precursors for toxin production; therefore, S. aureus can regulate the expression of virulent traits by modulating its metabolism. The pathogen's ability to adapt to available nutrients, survive the host immune response, and produce toxins is central to its persistence and pathogenicity.

The key metabolic pathways of S. aureus that provide energy and constitute the carbon pool, namely glycolysis and fermentation, the tricarboxylic acid (TCA) cycle, fatty acid, and amino acid metabolism, will be discussed. Adaptation to available nutrients requires proper nutrient sensing, which in S. aureus is mediated by two-component systems and global transcriptional regulators. Both nutrient sensing and metabolic flexibility have important roles in persistence and will therefore also be discussed. [4][5][6]

3. Metabolic Pathways in Staphylococcus aureus

The central pathways for energy generation and synthesis of metabolic precursors in Staphylococcus aureus include glycolysis, fermentation, the pentose phosphate pathway (PPP), the tricarboxylic acid (TCA) cycle, respiration, fatty acid biosynthesis (FASII), and amino acid metabolism. Metabolic flexibility—the ability to switch between these pathways or to activate them at different levels—allows S. aureus to utilize various nutrients in diverse host environments.

Glycolysis converts glucose into pyruvate, generating ATP through substrate-level phosphorylation and NADH. Under anaerobic conditions, pyruvate can be converted to lactate to regenerate NAD^+. Glucose-6-phosphate enters the PPP to generate NADPH and ribose-5-phosphate for anabolic reactions including nucleotide biosynthesis. In the presence of oxygen, pyruvate is further oxidized via the TCA cycle and coupled oxidative phosphorylation. The TCA cycle not only produces ATP but supplies biosynthetic building blocks; deficiencies in its intermediates strongly affect S. aureus colonization and virulence. [7][8]

3.1. Glycolysis and Fermentation

Staphylococcus aureus is a facultative anaerobic micro-organism capable of both aerobic and anaerobic respiration. Early in the infection process, the high glucose concentrations in the nasal mucosa, tissues, and blood allow S. aureus to rely primarily on glycolysis for energy production. During glycolysis, two ATP molecules are generated through substrate-level phosphorylation in the energy generation phase. Under conditions where the tricarboxylic acid (TCA) cycle cannot be activated due to low oxygen or low levels of TCA substrates, S. aureus reduces the glycolytic end product pyruvate to various toxic by-products through fermentation. During fermentation, pyruvate is converted to several by-products, including lactic acid, acetic acid, formic acid, ethanol, and carbon dioxide.

Several primary regulators contribute to a metabolic shift under such conditions. The SrrAB two-component system represses the expression of the TCA cycle genes in response to low-oxygen conditions, thereby promoting fermentation. The Catabolite control protein A is known to down-regulate respiration and up-regulate the genes encoding lactate dehydrogenase for the enhancement of glycolysis and fermentation, especially in the presence of high glucose concentrations. Moreover, during hypoxic growth, SaeRS, the primary regulator of many virulence factors, activates the expression of ldh1, a gene encoding lactate dehydrogenase. The

resulting lactic acid lowers the pH and kills the host cells, promoting tissue infection. [9][10][11]

3.2. TCA Cycle

The accumulation of glycolytic intermediates in S. aureus mutants with impaired TCA cycle activity indicates that carbon flow from glycolysis is interrupted, hampering efficient energy generation from these substrates and prompting a metabolic switch to other energy sources [12]. Therefore, the TCA cycle ostensibly provides the main source of NADH in post-exponential phase cells, supplying the substrate for the primary respiratory processes. Additionally, these cells can potentially maintain a considerable NADH supply by oxidizing amino acids or peptides derived from peptone or degraded proteins [13]. However, the cells become energy-limited when both the TCA cycle and fermentation pathways are inactive. These observations imply that both pathways significantly contribute to end-product formation, indicating the centrality of both in the cellular metabolism of S. aureus.

3.3. Fatty Acid Metabolism

An increased demand for membrane fatty acids must be met by de novo synthesis, which is encoded by the products of the highly conserved FASII pathway and termed the type II fatty acid synthase (FASII) pathway. In a relatively complex series of enzymatic reactions, two carbons derived from malonyl-ACP are added to the growing fatty acid chain in every elongation cycle until the final desired chain length is attained. S. aureus ATCC 6538 assembles branched-chain fatty acid chains. BCFAs can be anteiso- or iso-branched, with a methyl branch two carbons or one carbon, respectively, from the end of the fatty acid chain.

Considerable effort over recent years has been directed toward elucidating the distinct P. aeruginosa lipid biosynthesis, modification, and degradation pathways active during infection based on in vitro transcriptomics analyses or the chemical composition of isolated lipids. These findings are unsurprising considering recent results demonstrating that the P. aeruginosa lipidome is highly sensitive to nutrient availability.

3.4. Amino Acid Metabolism

Staphylococcus aureus metabolizes amino acids through degradation and synthesis pathways, adapting to environmental nutrient shifts. Aspartate biosynthesis or acquisition is necessary due to TCA cycle inhibition during staphylococcal infection and biofilm growth. Arginine residue catabolism occurs via the arginine deiminase pathway during biofilm growth. Glutamate metabolism interconnects multiple pathways including peptidoglycan synthesis, TCA cycle anaplerosis, polyamine biosynthesis, and the urea cycle. Catabolism of branched-chain amino acids generates branched-chain fatty acids in the membrane.

The mitochondrion-like role played by S. aureus aspartate and glutamate metabolism during biofilm growth is underscored by the need to repress transport systems for aspartate and glucose when glutamate uptake is impaired. These findings highlight that amino acid uptake can be critical for maintaining biofilm growth, especially when the TCA cycle is active. Although S. aureus is prototrophic for most amino acids, reported colonizers of the nose generally require tryptophan, methionine, and leucine. [14][15][16]

4. Nutrient Sensing Mechanisms

Staphylococcus aureus has a variety of signal transduction systems and regulatory proteins that allow detection of nutrient changes in the host microenvironment encountered during infection [17]. Nutrient availability differentially affects the expression of surface proteins and secreted virulence factors [1]. The ability of S. aureus to modulate metabolic flux as a function of available nutrients is essential for persistent infection.

Nutrient limitations encountered within a host compromise bacterial growth and present a barrier to infection. Several of these nutrient limitations prevent processing of metabolic intermediates that would be required to replenish biosynthetic pathways necessary for protein and DNA

synthesis. Adaptation to a nutrient-limiting environment contributes to the ability of S. aureus to persist and cause chronic infections. Metabolic regulators of S. aureus, like CodY, CcpA, and RpiRc, maintain metabolic homeostasis in response to abrupt environmental changes by sensing nutrient reservoirs. Nutrient-replete environments cause these regulators to repress metabolic and virulence genes, whereas nutrient-poor environments relieve this repression to upregulate selected metabolic and virulence genes.

4.1. Signal Transduction Pathways

Signal transduction pathways are a principal mechanism by which bacteria sense external changes and coordinate appropriate physiological responses. Although four major signal transduction pathways have been characterized in bacteria [18] , Staphylococcus aureus utilizes two—but mainly two-component—pathways when responding to environmental fluctuations. Two-component systems (TCSs) constitute one of the best-characterized adaptive tuning strategies in S. aureus when responding to nutritional and environmental changes. TCSs comprise both a membrane-bound kinase and a cytoplasmic response regulator that communicate to coordinate transcriptional programs, controlling genes necessary for bacterial survival, growth, and pathogenesis. S. aureus encodes 16 well-characterized TCSs, each functioning as a self-sufficient sensory unit capable of perceiving figurative environmental stimuli, such as changes in pH, oxygen availability, cell envelope status or amino acid pools, and nutrient availability. A paradigmatic sensor with a direct and major impact on metabolism and virulence is ArlRS: it governs classic virulence factors such as leucocidins and phenol-soluble modulin (PSM) toxins and contributes to adhesion and biofilm formation. Target promoters of ArlR, the response regulator, include the global regulators MgrA and Spx, and the resultant cascade strongly influences toxin production, surface protein expression, and metabolism. Consequently, ArlRS plays a significant role in S. aureus pathogenicity and disease, being implicated in a broad spectrum of conditions ranging from skin diseases to sepsis and endocarditis.

4.2. Regulatory Proteins

In S. aureus, regulatory proteins are crucial for adjusting metabolism in response to environmental nutrient availability and concentration. Nutrient shifts are sensed by two-component systems and other signal transduction pathways that integrate external and internal stimuli. The two central regulators of metabolism and virulence are CcpA, a major player in carbon-catabolite repression, and CodY, responsible for sensing branched-chain amino acids and GTP. Both regulators connect nutrient availability to virulence gene expression: CcpA promotes tissue colonisation and initiates invasive disease, while CodY suppresses tissue-destructive secreted virulence factors. Metabolic genes and virulence regulators are also controlled by the airSR system, which acts as a redox sensor.

In the absence of core-metabolic genes, toxin production and S. aureus persistence and virulence are altered, while some toxins directly interfere with the host’s energy metabolism. Analyses of these essential regulatory systems revealed that a strong link exists between metabolism and virulence gene expression. Therefore, S. aureus pathogenicity is highly dependent on metabolite concentrations. These regulatory mechanisms ultimately shape the outcome of S. aureus infection and influence the success of current treatment regimens. [19][2][20]

5. Metabolic Flexibility and Adaptation

The metabolic network of S. aureus demonstrates remarkable flexibility, allowing it to thrive in highly diverse niches with distinct nutritional demands. The characteristic golden pigment staphyloxanthin serves as a shield against a plethora of environmental stressors, including reactive oxygen species (ROS) generated by immune cells during infections. All other S. aureus metabolites are synthesized from the central carbon metabolism, and almost all metabolic pathways are interconnected. The function of these enzymes is largely conserved in all strains of S. aureus. During the last two decades, numerous studies have demonstrated how dynamics in

central metabolism influence S. aureus behavior. Nutrient availability during infection is a critical parameter. In limiting and stressful conditions, S. aureus can switch on and off different metabolic pathways to survive and maintain severe infections.

Rapid adaptation to nutrient availability in the host environment is crucial for bacterial persistence and pathogenicity. Studies have shown that metabolic flexibility correlates well with the survival and persistence of S. aureus during infections. Moreover, disruption of staphylococcal metabolic adaptation, either by blocking nutrient sensing systems or by depriving the bacterium of primary nutrient sources, cripples its ability to maintain persistent or chronic infections, making it more susceptible to host immune responses. These findings indicate that metabolic flexibility plays a key role in pathogenesis and influences disease outcome. Therefore, further elucidation of the metabolic mechanisms that delineate the metabolic niche of S. aureus during infection is essential for guiding the development of novel therapies against persistent and resistant infections. [21][8][22]

5.1. Environmental Influences

Temperature, pH value, and moisture have a great influence on S. aureus metabolic flexibility. In fact, impaired TCA cycle activity was only observed when S. aureus was grown aerobically at 37 °C and neutral pH, which corresponds to the human host environment. This indicates that flexible adaptation of S. aureus metabolism is an important property, allowing it to survive in a wide range of environments. The availability of nutrients is also a major force shaping bacterial physiology. The concentration of different nutritional sources such as glucose and amino acids in the microenvironment in which the bacteria multiply can be a nutrient supply as well as a signal that influences the expression of many genes, including those for virulence factors. The nutritional environment is often difficult for S. aureus to grow in during infection. Consequently, S. aureus has tolerance strategies to overcome these adverse environments. The nutrient limitation in abscesses is also amplified by the host immune response, which restricts the bioavailability of nutrients and minerals. [23][24][25]

5.2. Nutrient Availability

S. aureus possesses a suite of sensory mechanisms that facilitate the adaptation of its metabolism to external nutrient availability. Prominent among these are the serine/threonine kinase-phosphatase pairs Stk1/Stp1 and GlnR/GlnR1, which modulate the activity of transcriptional regulators involved in the control of nutrient-scavenging pathways [1]. Iron-responsive transcription factors such as Fur and Zur regulate the expression of systems involved in the uptake of iron and zinc, because these metals are essential for pathogenicity [17]. The activity of the transition-metal-sensing repressor CzrA also connects cellular metal homeostasis to oxidative stress and the DNA-damage response. Nutrient-sensitive regulators such as CcpA (glucose and carbon source) and CodY (branched-chain amino acids) help to coordinate virulence factor expression with metabolic status.

6. Role of Metabolic Flexibility in Persistence

S. aureus's metabolic flexibility is strongly linked to its ability to persist in different infection settings. Carbohydrate starvation and respiratory inhibition induce biofilm formation in S. aureus and S. epidermidis [1]. In rabbits with conductive keratoplasty wounds, S. aureus persists for infection following treatment with antibiotics downregulated the expression of proteins involved in carbohydrate fermentation and the TCA cycle, likely forcing the bacteria to adapt to ATP depletion by activating alternative pathways [26]. During kidney abscess formation in a murine model, proteomic data suggest that S. aureus responds to a hypoxic environment by limiting the carbon flux through the TCA cycle. Instead, the bacteria appear to use overflow metabolism, driven by glucose fermentation, to form lactate, which macrophages use as a carbon source to enhance IL-10 production and attenuate the host immune response.

6.1. Biofilm Formation

The formation of biofilms linked to persistence is influenced by metabolic flexibility and adaptation to hostile conditions, ultimately determining bacterial fitness. Spontaneous mutations can contribute to the generation of stable small colony variant (SCV) strains with altered biofilm-forming capacities. SCV biofilms are generated more rapidly and are significantly thicker compared with their wild-type counterparts, primarily due to the up-regulation of capsular polysaccharide synthesis [1]. The enhanced polysaccharide matrix is a crucial virulence factor for coagulase-negative staphylococci (CNS) because it promotes adherence and surface colonization in device-related infections. The combination of the SCV phenotype and hyper-biofilm formation produces a bacterial community highly adept at sustaining relapsing implant-associated infections that are difficult to eradicate with chemotherapy, often necessitating medical device removal. Because the SCV phenotype is phenotypically determined, the characteristics are transient and can revert to the wild-type state, contributing to the resurgence of infections even years after the initial episode. The SCV phenotype represents a cost-effective survival strategy that enhances persistence under various environmental conditions, particularly for pathogens such as staphylococci. Under stress conditions, increased synthesis of amino acids, fatty acids, and phospholipids helps maintain homeostasis and supports survival within infection niches. Such metabolic remodelling can also induce physiological changes like cell wall thickening, which confers cross-protection against multiple stresses. Consistent with transcriptional-profiling studies of S. aureus biofilms, bacteria grow under microaerobic or anaerobic conditions, as evidenced by increased expression of genes associated with arginine deimination, mixed-acid fermentation pathways, and pyruvate formate lyase [12]. Anaerobiosis enhances biofilm formation and stimulates the synthesis of polysaccharide intercellular adhesin. Biofilm formation is regulated in response to nutrient availability, oxygen tension, and stress. These environmental factors influence the metabolic status, thereby modulating virulence and biofilm-forming capacity. Bacterial biofilms facilitate survival, prolong infections, and hinder patient recovery. S. aureus forms persistent biofilms that show resistance to antibiotics and environmental stresses. Global transcriptomic analysis of the early stage of biofilm formation across multiple clonal lineages reveals a set of core transcriptional benchmarks, including a shift toward anaerobic respiration and reduced translational capacity, which may occur earlier than previously anticipated [27]. This metabolic adaptation contributes to increased antibiotic tolerance and persistence. Biofilms exhibit similar regulation of attachment factors, underscoring the potential for anti-biofilm surfaces and coatings. Regulatory factors controlling initial attachment—VraG, GraR, MprF, and DltABCD—are promising targets for biofilm-prevention strategies. The strain-specific regulation of virulence and attachment factors reflects the diverse infection strategies employed by S. aureus. This understanding of the regulatory landscape driving biofilm development better informs the design of effective anti-biofilm therapeutics.

6.2. Survival in Host Environments

Staphylococci are highly successful at colonizing multiple environments, from terrestrial to host-associated niches, including harsh clinical settings, where unresolved infection remains a public health concern [1]. Their ability to survive and persist under a broad range of transient or long-term bacteriostatic and bactericidal conditions is linked to metabolic versatility that enables rapid adaption and cellular homeostasis. The metabolic capability for quick modulation facilitates acclimatization and persistence on a global scale. Studying Staphylococcus metabolic behaviour therefore provides insight into survival and persistence under relevant environmental and clinical conditions.

S. aureus is an opportunistic pathogen in the environment and on human skin, mouth, and gastrointestinal tract. It grows under conditions that would preclude survival or replication of competing microorganisms and is able to persist within diverse host and environmental microhabitats. The ability to successfully adapt and grow in such host microenvironments with discrete and sometimes limited nutrients is linked to the metabolic flexibility of the organism and

its wide range of virulence traits. These traits mediate survival at the interface of commensalism and host infection throughout the host life cycle.

7. Pathogenicity and Virulence Factors

The ability of Staphylococcus aureus to adapt to changing nutrient conditions contributes not only to its persistence within the host but also to the production of virulence factors, which enable the establishment of infections and evasion from the immune system. Studies on toxin production emerging from central metabolism began 2 decades ago with the investigation of the amino acid response. It was observed that deficiencies of the branched-chain amino acids (BCAAs) isoleucine and valine led to the induction of the Agr system in the absence of its autoinducing peptide (AIP). Subsequent studies revealed that AgrA can be phosphorylated in the absence of AIP and that low intracellular BCAA pools during infection may lead to increased RNAIII expression remarkably early in the host.

A recent study has also linked the TCA cycle to Agr. Both pH and glucose levels regulate the Agr system, wherein acidic pH inhibits Agr while glucose potentiates it. However, the pH effect requires glucose and the TCA cycle for Agr repression. Addition of acetic acid to a medium buffered to pH 7.0 leads to complete repression of the Agr system. Further, the intracellular pH is also lowered in response to glucose depletion, resulting in Agr repression. Intracellular acidification decreased AgrA binding to the P2 and P3 promoters, which was rescued by addition of glucose. Thus, the Agr system is modulated by intracellular pH through a complex interaction between glycolysis, glucose depletion, and the TCA cycle.

7.1. Toxins and Enzymes

The expression of virulence determinants is a vital step in establishing an acute S. aureus infection. Many toxins and damaging enzymes have therefore evolved to cause tissue damage and lyse host cells, as the resulting release of nutrients is an essential source of carbon and nitrogen. Expression of these secreted virulence factors is tightly regulated according to environmental cues. Small amounts of honey added to the growth medium have been shown to delay S. aureus growth and partially inhibit the quorum lectin Agr. Secreted exotoxins such as α-hemolysin and staphylococcal superantigen-like 1 were then downregulated, resulting in reduced haemolytic activity.

In vivo, the metabolic profile of catheters infected with two different clinical MRSA strains was determined. In association with the expression of fibrinogen binding protein and central carbon metabolic enzymes, the highly pathogenic type USA300 tended to produce much higher levels of toxins and enzymes than the type USA400. Nonetheless, the two strains shared a central core metabolism that supported growth, persistence and anchoring for infection. [28][29][30]

7.2. Immune Evasion Strategies

S. aureus evasion of the host immune response is a critical factor in its pathogenesis and persistence. This pathogen employs several techniques to circumvent neutrophil killing: it can survive inside neutrophils, inhibit neutrophil recruitment, induce neutrophil apoptosis, and lyse neutrophils. Metabolic activation is closely linked to the production of virulence factors responsible for these immune evasion strategies. Activated neutrophils exhibit an NOX2-dependent antimicrobial response that activates S. aureus virulence, thereby facilitating host colonization. Additionally, several virulence factors of S. aureus are regulated by toxin-antitoxin systems. These toxins inhibit multiple cellular processes of the host and must be tightly regulated to prevent increased host mortality despite their roles in immune response modulation and bacterial persistence.

Various signal transduction systems are involved in sensing nutritional stress, ultimately regulating virulence factor expression. The TCA cycle of S. aureus has been implicated in the modulation of virulence, suggesting that carbon source availability and S. aureus metabolism

influence immune evasion through the regulation of virulence. These findings highlight a close connection between immune evasion and metabolic flexibility in S. aureus, underscoring the central role of nutrient adaptation in the persistence and pathogenicity of the bacterium. [31][8][7]

8. Clinical Implications

Staphylococci pose a significant public health threat by causing community-acquired and nosocomial infections. Their ability to survive and persist despite growth limitations, exposure to hostile conditions, and bactericidal measures is linked to metabolic adaptation [1]. The metabolic versatility of staphylococci—manifested in their ability to shift between respiratory and fermentative metabolism in the presence or absence of oxygen—allows rapid adaptive responses to transient or long-term bacteriostatic and bactericidal conditions, contributing to their widespread dissemination and difficulty in eradication.

8.1. Antibiotic Resistance

Bacterial resistance to antibiotics is a critical challenge in infection management, especially due to the scarcity of new antimicrobial compounds and the rampant overuse of existing drugs. Staphylococci often withstand antimicrobial treatment and persist in the host as drug-tolerant subpopulations when targeted by antibiotics [1]. Several features contribute to enhanced antimicrobial tolerance, including protection by the extracellular matrix in biofilms, alterations to the cell wall, upregulated stress response pathways, and reduction of bacterial intracellular energy. Staphylococci readily develop mutations within mono-culture biofilms, with prolonged antibiotic exposure further selecting for resistant strains. The intracellular and biofilm-associated nature of staphylococci also reduces the cellular concentrations of antimicrobials below the amount needed for rapid killing, facilitating bacterial adaptation.

8.2. Treatment Strategies

Population heterogeneity constitutes an emergent resistance strategy that enables rapid survival during exposure to lethal conditions. Subpopulations of a clonal culture can assume distinct physiological roles, permitting adaptation of the community to environmental changes [1]. Staphylococci survive environmental assaults behind the physical and nutritional barrier of biofilms. Stationary phase and biofilm cells endure environmental stresses better than exponential-phase cultures and exhibit elevated minimum bactericidal concentrations. These studies reveal metabolic characteristics facilitating persistence and tolerance in staphylococci and illustrate links between the metabolic state of cells and antibiotic resistance. Combination therapies facilitate effective eradication of persistent cells but require consideration of drug–drug interactions and toxicity. Treatment of persisters with reagents targeting membrane integrity or respiration, combined with conventional antibiotics or antimicrobial peptides, offers a promising strategy because such reagents are effective against metabolically inactive cells. Repurposing drugs with well-known safety profiles, in combination with antibiotics, provides an achievable approach to combating persistent biofilm infections and antibiotic-refractory infections.

9. Research Methodologies

Experimental studies have contributed substantially towards understanding the complexity of S. aureus metabolism and the regulation of adaptive responses. Experiments are typically conducted in three stages, beginning with the characterization of growth in a given condition or medium, followed by RNA and metabolite extraction at key growth phases, and finally analysis of the isolated material. An example of the first step involves the use of S. aureus in a flow cell apparatus where oxygen depletion triggers the production of the metabolite, phenol-soluble modulins, from planktonic cultures on glass slides. Overall, research techniques employ a combination of in vitro experimentation, sophisticated molecular approaches and in vivo infection models [1].

9.1. In Vitro Studies

An array of in vitro assays has enabled mechanistic studies deciphering metabolic adaptations in

Staphylococcus aureus [1]. S. aureus displays metabolic versatility, rapidly readjusting its central metabolic pathways and synthesis of organic osmolytes in response to external nutrient availability. The pathogen's metabolic diversity profoundly affects key cellular processes, influencing the expression of host colonisation and virulence determinants.

9.2. In Vivo Models

In vivo models have been invaluable tools for investigating the pathogenesis of S. aureus together with mechanisms of metabolism and persistence. Different models have been developed, ranging from the use of mice to study arthritis , abscess formation , ear infections , sepsis and pneumonia to Caenorhabditis elegans and Drosophila melanogaster for an investigation of general toxicity and host-pathogen interaction. A number of different protocols have been validated, which can be tailored to different experimental requirements.

9.3. Genomic and Proteomic Approaches

Omics approaches have been widely used to elucidate the metabolic networks supporting staphylococcal infection and persistence. For example, comparative proteomics showed that isolates of Staphylococcus aureus (S. aureus) that cause prosthetic joint infections have well-developed fermentative metabolism and upregulate the pentose phosphate pathway during periods of nutrient-poor growth [1]. In the context of a liberal infection site model, studies of cytoplasmic and secreted proteins revealed S. aureus adapts its metabolism homeostatically in response to changes in environmental conditions [32].

10. Future Directions in Research

Future research on the metabolic flexibility of Staphylococcus aureus should focus on targeting metabolic pathways that support its survival and pathogenicity. Identifying specific metabolites or pathways responsible for phenotypic shifts enables the development of interventions to limit persistence and virulence. Novel diagnostic tools that rapidly detect altered metabolic states facilitate timely and accurate diagnosis and improve clinical outcomes. While the majority of studies concentrate on S. aureus, expanding research to other pathogenic staphylococci will clarify their roles in infections and resistance development [1].

A comprehensive understanding of the metabolic interplay between S. aureus and host immunity remains a key priority. Elucidating the mechanisms by which the pathogen senses, adapts to, and competes for nutrients within the host environment will deepen insights into its persistence strategies and virulence. The role of immunometabolism in shaping infection dynamics offers additional avenues to disrupt bacterial survival. Questions include how metabolic reprogramming of host immune cells influences bacterial clearance, the impact of host-derived metabolites on bacterial virulence factor expression, and the pathways enabling S. aureus to adjust to immunological cues [26].

Continuing to integrate metabolic investigations with studies of host–pathogen interactions promises to inform the development of therapies that simultaneously target bacterial metabolism and bolster host immune responses. Such approaches are critical to overcoming the significant health burden posed by persistent S. aureus infections. [33][34][35]

10.1. Targeting Metabolic Pathways

Several antimicrobial strategies incorporated in therapeutic regimes that target S. aureus have been identified. Given the importance of functional and active glycolysis to biofilm survival, the test compounds xanthohumol and pyridinyl imidazole were investigated for their biofilm antimicrobial effect. These data revealed that both compounds likely exert their effects via interference with glycolysis underlining the potential of targeting metabolic pathways as an approach for identification of novel antimicrobial strategies. With indications that S. aureus generates ATP through other means during non-biofilm survival, inhibition of these non-glycolytic ATP sources drove examination of alternative energy-generating pathways as therapeutic targets. Indeed,

several non-glycolytic ATP synthesis pathways have been suggested for S. aureus, including amino acid catabolism and phosphotransacetylase-dependent acetate metabolism.

The metabolism of seven amino acids has been linked to S. aureus pathogenesis with expression of their catabolic genes induced during-in vivo infection models. Consistent with this, two essential amino acid catabolizing enzymes, proline dehydrogenase (PutA) and arginine deiminase, are regulated by arginine catabolic element repressor (AcuR; further reviewed in Section 4.2), which in turn is controlled by the FadR-related transcriptional regulator (SAUSA300_1148) that suppresses purine synthesis during-i-n vivo infection. When these two enzymes were assessed for biofilm viability in the presence of the drug 3-aminooxy-propionic acid, the inhibition of these pathways reduced non-glycolytic ATP production considerably, supporting the established role of amino acid catabolism in non-glycolytic assay conditions. The phosphotransacetylase (Pta) enzyme has also been examined for its role in central metabolism and pathogenesis with inactivation of pta shown to alter biofilm formation. Furthermore, disruption of Pta enzyme activity can prevent expression of key virulence factors and suppress bacterial growth in a murine pneumonia model. Beyond targeting the unique features of S. aureus metabolism, compounds that target host metabolism offer a means by which bacterial survival could be restricted by limiting nutrient availability or through altering factors such as host temperature. Indeed, catecholamine drugs, such as dobutamine and norepinephrine, which lower host temperature, have been deemed promising candidates for antimicrobial therapy. [36][37][38]

10.2. Understanding Host Interaction

The host environment is a complex niche that S. aureus must rapidly sense and respond to in order to adapt [1]. The detection of host environmental conditions serves as a pivotal signal to modulate metabolic shifts, ensuring successful colonisation and persistence. Subsequently, the ability to sense and respond to changes in nutrient availability remains paramount for the survival of the bacterium under varying environmental conditions encountered during infection and transmission. The direct coupling of environmental sensing to the activation and repression of metabolic pathways underpins the capacity of S. aureus to adapt its metabolism to suit changing nutrient availabilities [17]. These metabolic adjustments underpin the ability to establish infections at distinct host sites, as well as the successful colonisation of hospital environments by these formidable pathogens. Understanding the interplay between these processes is crucial to unravel the broader role of metabolic flexibility in S. aureus pathogenesis.

11. Discussion

As a facultative anaerobic pathogen, Staphylococcus aureus colonized the human nose in the beginning and moved from the human nose to many harsh environments around the world. S. aureus developed metabolic flexibility in response to environmental fixation. This metabolic flexibility not only helps S. aureus adapt to change but involuntarily strengthens their metabolic persistence and pathogenicity. S. aureus can use a variety of carbon sources, including glycolysis, fermentation, pentose phosphate pathway (PPP), tricarboxylic acid cycle (TCA), fatty acid, and amino acid metabolism. It can also control the metabolism of carbon sources to avoid overoxidation of the current pathway and make metabolism more efficient. All these metabolic abilities are also inseparable from the efficient sensing/response system, including two-component signal transduction system (TCSs), transcription factors, and their following metabolic pathways.

In summary, the metabolism of S. aureus has been the focus concern from early explorations of metabolic pathway to recent ones of persistence and virulence. The flexibility of metabolic pathway not only ensures the growth and survival of S. aureus but also affects persistence and virulence. Therefore, the metabolism of S. aureus at the local level is of great importance. In-depth study of the metabolic pathway of S. aureus will undoubtedly become an important direction to understand the interaction between S. aureus and host. Looking for the similarities and differences of metabolic function between S. aureus and host is likely to weaken the metabolic persistence and pathogenicity of S. aureus while having little damage on the local metabolic balance of the host.

[39][8][2]

12. Limitations of Current Research

Despite notable advances in understanding the metabolic flexibility of Staphylococcus aureus, significant gaps remain. Research predominantly concentrates on S. aureus, with less attention to other clinically relevant staphylococci. The influence of impaired or altered metabolic activity on pathogenicity also is insufficiently understood [1]. Investigating additional species may clarify whether common adaptive mechanisms drive persistence and disease manifestations across the genus.

Metabolic flexibility influences pathogenicity through effects on extracellular polysaccharide production, toxin biosynthesis, host colonization, and immune evasion. Nevertheless, current knowledge of this relationship is incomplete, particularly concerning the interplay between effectors and regulators [26]. Moreover, the dynamic host environment imposes selective pressures that shape nutrient preferences and metabolic robustness. Little is known about how S. aureus adapts its metabolic processes to such fluctuations or whether preferences shift with changes in host immunity or nutrient availability. Enhancing insight into these areas could facilitate the development of therapeutic agents targeting critical metabolic pathways and specific regulators.

13. Ethical Considerations

S. aureus infections present major and increasing therapeutic challenges. The plasticity of S. aureus virulence and metabolism has permitted its adaptation to multiple hosts, body sites, and selective pressures ranging from antibiotic stress to immune responses. However, the ability of S. aureus to effectively adapt to its environment constitutes a crucial property that impedes infection treatment and resolution. Its metabolic flexibility, representing the capacity of this pathogen to utilize a variety of nutrients to sustain growth, not only contributes to its ability to survive under adverse conditions but also provides the basis for its commensal relationship with the host. In fact, nutrient adaptation provides the linkage between persistence and pathogenicity.

The wide metabolic repertoire of S. aureus is directly responsible for its successful colonization of distinct body sites and hosts. Two main aspects emerge in the host–pathogen relationship: the ability to resist bacterial elimination strategies and the capacity to face nutrient starvation within highly competitive environments. Nutrient responsiveness is therefore the central feature of metabolic flexibility, enabling S. aureus to shift between fermentation and respiration, utilize carbon sources such as glucose or amino acids, switch between fatty acid biosynthesis and exogenous fatty acid incorporation, and redirect amino acid metabolism through the TCA cycle and gluconeogenesis. S. aureus possesses various signaling networks to detect changes in the external nutrient environment, allowing it to promptly affect gene expression and protein activity accordingly. Metabolic flexibility, as the metabolic adaptation controlled and implemented through specific regulatory systems, represents the key for ongoing survival and host adaptation. [7][2][40]

14. Conclusion

The survival and persistence of Staphylococci in diverse environments and across microbial habitats underlie their success as pathogens with a major public health impact. Their metabolic versatility enables rapid adaptation and switch between metabolic states optimized for bacteriostatic or bactericidal conditions. Community structure adds another level of protection against antimicrobial compounds, and protective alteration of antimicrobial targets also play an important role in persistence. Study of microbial behavior at the metabolite level provides key information on the mechanisms regulating survival and persistence. Staphylococci are unique among human pathogens in that they circulate widely in the general environment, and highly adapted strains subsequently enter the human population and increase the level of disease. Alteration of physiology enabled through metabolic modifications is an important mechanism of

adaptation and niche exploitation. Metabolic flexibility therefore has a two-fold effect—it enhances fitness in the face of challenge and increases the capacity to persist within a niche, and it facilitates spread and circulation between environments and between hosts. Ultimately, this influences their pathogenicity and contributes to the success of Staphylococci as infectious agents.

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