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Review

Dextrin utilization in *Streptococcus pyogenes* pathogenesis and growth

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ABSTRACT

Background: *Streptococcus pyogenes* has several clinical manifestations, from mild pharyngitis to life-threatening necrotizing fasciitis. Nutrient conditions strongly influence its virulence, and the ability to metabolize dextrin contributes to growth and pathogenicity. Since dextrin-dependent phenotypes link metabolic adaptation with virulence regulation, reviewing the current knowledge is essential for understanding how carbohydrate utilization shapes *S. pyogenes* pathogenesis and proliferation.

Highlight: Animal models have demonstrated that the maltose/dextrin utilization operon enhances fitness and is co-activated with major toxins at infection sites. System-level analyses have shown that dextrin induces the *nga–ifs–slo* operon and activates CovRS-associated modules, a regulatory system central to virulence control. Dextrin also promotes *in vitro* growth, with genome-scale metabolic modeling implicating increased arginine metabolism in this phenotype. Collectively, these results suggest that dextrin acts as a regulatory cue to reprogram virulence and metabolic capacity.

Conclusion: Dextrin utilization shapes both the growth and virulence of *S. pyogenes*. Although the mechanisms remain incompletely defined, integrating metabolic modeling with experimental approaches will be crucial for clarifying how carbohydrate use drives invasive diseases.

1. Introduction

Streptococcus pyogenes is a major human pathogen responsible for more than 700 million infections and at least 517,000 deaths annually worldwide [1]. It causes diseases ranging from pharyngitis and skin infections to invasive syndromes such as sepsis, necrotizing fasciitis, and toxic shock. During infection, bacteria encounter host cells, immune defenses, and nutrient shifts that differ markedly from laboratory media.

Dextrin, a plant-derived glucose polysaccharide, is not a natural nutrient at most infection sites, although starch breakdown may transiently appear in the pharynx. Still, components of the maltose/dextrin utilization operon are linked to disease progression in a cynomolgus macaque necrotizing myositis model [2]. Furthermore, our work in a murine necrotizing fasciitis model showed the operon is strongly induced at local infection sites [3].These findings suggest that the maltose/dextrin utilization contributes to *S. pyogenes* pathogenic potential. Elucidating this connection could reveal new strategies to control invasive disease.

2. Maltose/dextrin utilization operon and the regulation

Fig. 1 illustrates the genetic organization of the maltose/dextrin utilization operon, while Table 1 summarizes the functional roles of the individual genes encoded within this locus. Previous studies have shown that the transcriptional repressor MalR regulates genes such as *glgP, malQ, malR, malE, malF, malG, pulA,* and *malt* [4,5], whereas MalR2 controls *malA, malD, malC, amyA, amyB, malX, malF,* and *malG* [5,6]. However, as summarized in Table 2, the maltose/dextrin utilization operon is subject to regulation by multiple transcription factors.

In the M1 serotype, this operon is regulated by CcpA, a transcriptional regulator mediating carbon catabolite repression while also controlling virulence factors such as toxins and enzymes [7]. It is further controlled by CovRS, a two-component system that represses virulence genes and modulates metabolism in response to environmental signals [8,9]. Additionally, in the M1 serotype background, maltose/dextrin utilization operon is influenced by Mga, a stand-alone global regulator that activates core virulence genes and links carbohydrate availability to pathogenesis [10], as well as by TrxSR, a two-component system that

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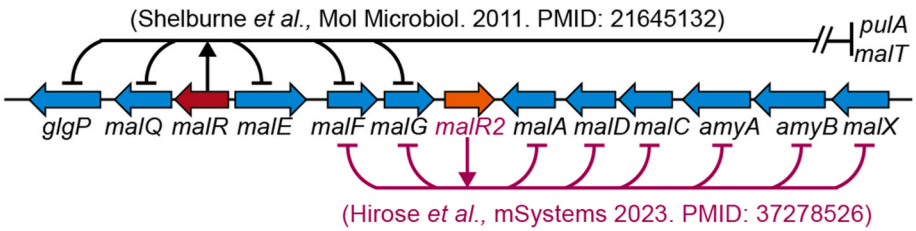

Fig. 1. Genetic organization of the maltose/dextrin utilization operon in *Streptococcus pyogenes* M1 serotype.
The operon consists of multiple genes involved in maltose and dextrin metabolism. MalR regulates genes such as *glgP, malQ, malR, malE, malF, malG, pulA,* and *malT*, whereas MalR2 controls *malA, malD, malC, amyA, amyB, malX, malF,* and *malG*.

Table 1
Gene information of the maltose/dextrin utilization operons.

Gene name	Accession ID in GenBank			Definition
	CP008776.1	CP000017.2	CP160045.1	
glgP	SP5448_04340	M5005_Spy1055	SPy_1291	Maltodextrin phosphorylase (EC 2.4.1.1)
malQ	SP5448_04335	M5005_Spy1056	SPy_1292	4-alpha-glucanotransferase (amylomaltase) (EC 2.4.1.25)
malR	SP5448_04330	M5005_Spy1057	SPy_1293	Maltose operon transcriptional repressor MalR, LacI family
malE	SP5448_04325	M5005_Spy1058	SPy_1294	Maltodextrin ABC transporter, substrate-binding protein MdxE
malF	SP5448_04320	M5005_Spy1059	SPy_1295	Maltodextrin ABC transporter, permease protein MdxF
malG	SP5448_04315	M5005_Spy1060	SPy_1296	Maltodextrin ABC transporter, permease protein MdxG
malR2	SP5448_04310	M5005_Spy1061	SPy_1297	Transcriptional regulator, LacI family
malA	SP5448_04305	M5005_Spy1062	SPy_1298	Maltodextrose utilization protein YvdJ
malD	SP5448_04300	M5005_Spy1063	SPy_1299	Maltodextrin ABC transporter, permease protein MdxG
malC	SP5448_04295	M5005_Spy1064	SPy_1301	Maltodextrin ABC transporter, permease protein MdxF
amyA	SP5448_04290	M5005_Spy1065	SPy_1302	Cyclomaltodextrin glucanotransferase (EC 2.4.1.19)
amyB	SP5448_04285	M5005_Spy1066	SPy_1304	Neopullulanase (EC 3.2.1.135)
malX	SP5448_04275	M5005_Spy1067	SPy_1306	Maltodextrin ABC transporter, substrate-binding protein MdxE

Table 2
Transcription factors involved in the regulation of maltose/dextrin utilization operons.

Transcription factors involved in regulation	Serotype	Strain	Regulated genes	Medium	Condition	Publication
CcpA	M1	SF370	*malE, malF, malG, malA, malD, malC, amyA, amyB, malX*	Non	Non	RegPrecise [5]
MalR	M1	SF370	*glgP, malQ, malR, malE, malF, malG*	Non	Non	RegPrecise [5]
MalR2	M1	SF370	*malA, malD, malC, amyA, amyB, malX*	Non	Non	RegPrecise [5]
CovRS (LE)	M1	MGAS5005	*malE*	THY	Late-exponential	[8]
CovRS (ME)	M1	MGAS5005	*malE*	THY	Mid-exponential	[8]
CovRS	M1	MGAS2221	*malQ, malF, malG*	THY	Stationary	[9]
CovRS/CcpA (double knockout)	M1	MGAS2221	*glgP, malR2, malA, malD, malC, amyA, amyB, malX*	THY	Non	[9]
Ihk-Irr	M6	JRS4	*malQ, malG*	THY	Late-exponential	[14]
MalR	M1	MGAS2221	*glgP, malQ, malE, malF, malG*	THY	Exponential	[4]
Mga	M1	5448	*malF, malA, malD, malC, amyA, amyB, malX*	THY vs C media	High glucose	[10]
Nra	M49	591	*malE, malF, malG, malA*	THY	Transition phase	[12]
Rgg	M49	NZ131	*malA*	THY	Exponetional	[13]
Rgg	M49	NZ131	*glgP, malE, malF, malG, malR2, malC, amyA*	THY	Post-exponential	[13]
TrxSR	M1	MGAS5005	*malG, amyA, amyB*	DMEM supplemented with the asparagine	Incubated for 6 h	[11]

THY: Todd Hewitt broth supplemented with yeast extract.

senses host-derived asparagine and modulates the expression of virulence and metabolic genes [11].

In other serotypes, additional regulatory inputs have been described. For example, in M49 strains, Nra, a RofA-like regulator that represses pilus and multiple virulence genes while activating metabolic functions [12], and Rgg, a stand-alone global regulator of non-glucose carbohydrate utilization [13], both regulate the maltose/dextrin utilization operon. In M6 strains, the operon is regulated by Ihk-Irr, a two-component transcriptional regulator that senses neutrophil-derived stress and promotes cell wall synthesis [14]. Collectively, these findings indicate that the maltose/dextrin utilization operon is subject to diverse and multilayered regulation, suggesting that its expression is dynamically tuned to the environmental conditions encountered by the pathogen.

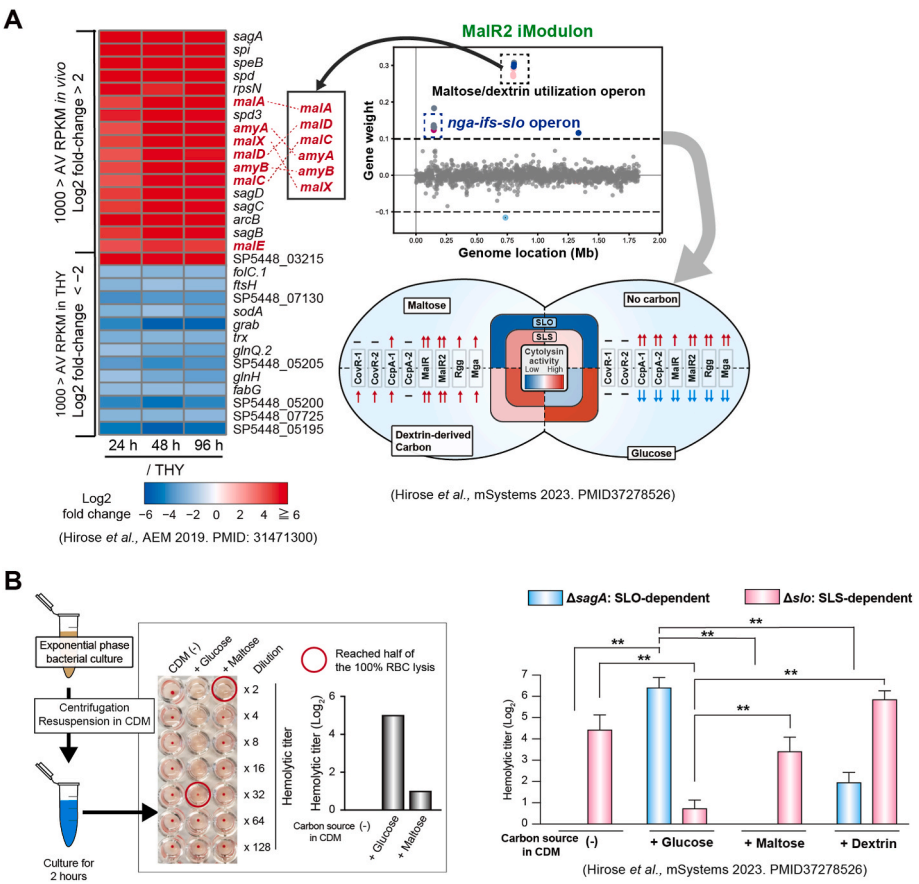

Fig. 2. Maltose/dextrin operon activated in mouse necrotizing fasciitis model consists of MalR2 iModulon and is related to dextrin-dependent Streptolysin O activities. A. (Left) RNA-seq analysis in a murine necrotizing fasciitis model showed that genes of the maltose/dextrin utilization operon (*malA, malD, malC, amyA, amyB,* and *malX*) were significantly upregulated *in vivo* compared with exponential-phase growth in Todd–Hewitt broth supplemented with yeast extract (THY). These genes were co-induced with major virulence genes such as *sagA* (SLS), *speB* (cysteine protease), and *spd* (DNase). (Upper right) Independent component analysis identified the MalR2 iModulon, which includes both the maltose/dextrin operon and the *nga-ifs-slo* virulence operon encoding NADase and streptolysin O, suggesting their coordinated regulation. (Bottom right) Schematic diagram illustrating how different carbon sources influence transcriptional regulation and hemolytic activity in *S. pyogenes.* Glucose supplementation supports only SLO-dependent hemolysis, whereas maltose induces exclusively SLS-dependent hemolysis. In contrast, dextrin supplementation enhances both SLS- and SLO-mediated hemolytic activities. Transcriptome-based iModulon analysis further revealed that dextrin specifically increases the activity of the MalR2 iModulon, which contains the *nga-ifs-slo* operon, as well as CovR-related iModulons that are central regulators of virulence. Together, these findings indicate that dextrin utilization not only alters functional toxin expression but also reprograms regulatory modules controlling virulence and metabolism. B. (Left) Experimental workflow for red blood cell hemolysis assay. Each titer was recorded as the point that the hemolysis reached half of the 100 % RBC lysis (H2O) control. No bacteria controls were used as the 0 % RBC lysis. (Right) Hemolytic activity of the whole culture from Δ*sagA* and Δ*slo* strains. Assay was conducted in biological duplicates and repeated six times. Values are presented as the mean of duplicates from a representative experiment. The *sagA* encodes the precursor peptide of SLS, and *slo* encodes SLO.

3. Contribution of the maltose/dextrin utilization operon at necrotizing fasciitis infection sites

Genome-wide transposon mutagenesis analyses have revealed that the maltose/dextrin utilization operon contributes to the fitness and virulence of *S. pyogenes* during invasive infections. Transposon-directed insertion-site sequencing (TraDIS) in a nonhuman primate (NHP) model of necrotizing myositis identified multiple transporters, including those involved in carbohydrate metabolism such as *malE* and *malG*, as essential for infection [2]. Moreover, disruption of genes for these components or of MalR, a LacI-family transcriptional regulator that represses maltose/dextrin utilization, significantly impaired *S. pyogenes* virulence in the NHP model, underscoring the critical role of maltose/dextrin metabolism in disease progression.

In a separate study, transcriptomic analyses using a murine necrotizing fasciitis model demonstrated marked *in vivo* upregulation of maltose/dextrin utilization genes [3] (Fig. 2A, left). RNA-seq profiling revealed that *malA, malD, malC, amyA, amyB,* and *malX* were significantly upregulated at all examined time points (24, 48, and 96 h postinfection) compared with exponential growth in Todd-Hewitt broth supplemented with yeast extract (THY). As illustrated in Fig. 2A (left), these genes were among the most highly upregulated genes, together with encoding well-known virulence determinants such as *sagA* (streptolysin S), *speB* (cysteine protease), and *spd* (streptococcal extracellular DNase). These findings suggest that the maltose/dextrin utilization operon is co-activated with major toxins during infection, highlighting its relevance to bacterial survival and tissue destruction in the inflamed host niche.

4. Dextrin utilization in *S. pyogenes* upregulates the *nga-ifs-slo* operon and induces SLS- and SLO-dependent hemolytic activity

To systematically analyze the transcriptional regulatory network of *S. pyogenes*, we applied independent component analysis (ICA) to a large compendium of RNA-seq data from the serotype M1 strain [6]. This approach identified independently modulated sets of genes, termed iModulons, which represent data-driven regulons inferred directly from transcriptome profiles [15–17]. Among the 42 iModulons discovered,

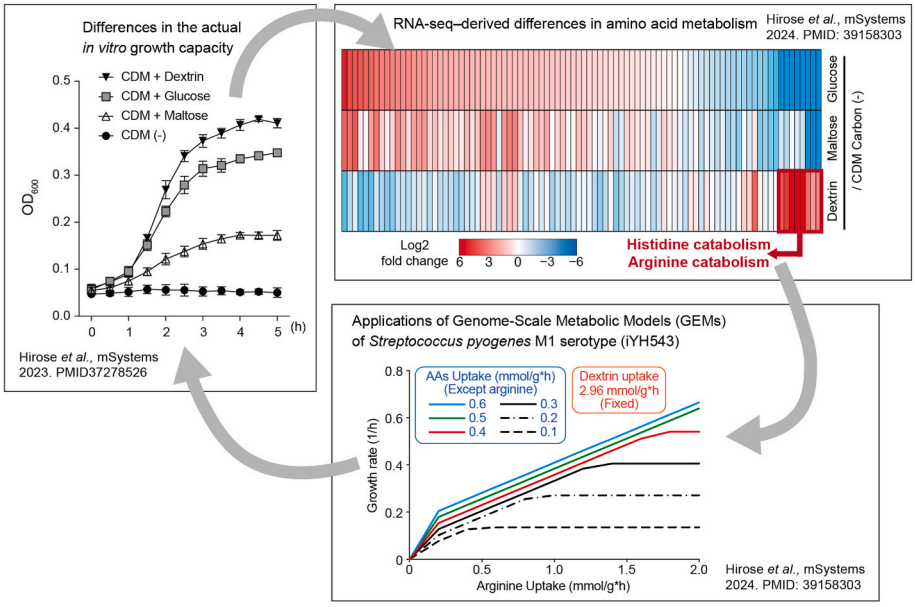

Fig. 3. Dextrin-dependent growth enhancement of *S. pyogenes* strain 5448 and its association with arginine metabolism. (Left) *In vitro* growth assays in chemically defined medium (CDM) supplemented with different carbon sources demonstrated that dextrin supported stronger bacterial growth compared with glucose, maltose, or CDM without supplementation. (Upper right) Transcriptomic profiling revealed that bacterial utilization of dextrin in CDM induced marked changes in amino acid metabolism compared with CDM glucose or maltose conditions. Notably, genes involved in arginine and histidine catabolism were strongly upregulated under dextrin conditions. (Bottom right) Genome-scale metabolic modeling (GEM; model iYH543) combined with flux balance analysis (FBA) was used to evaluate the contribution of arginine uptake to bacterial growth. Simulations showed that, even when the uptake of other amino acids was constrained, increasing arginine uptake led to higher predicted biomass yields.

one notable set was the MalR2 iModulon, which contains genes of the maltose/dextrin utilization operon (*malA, malD, malC, amyA, amyB,* and *malX*) as well as the *nga-ifs-slo* operon encoding the potent virulence factors NADase (*nga*), its immunity factor (*ifs*), and streptolysin O (*slo*) (Fig. 2A, upper right) [6].

When *S. pyogenes* was cultured in chemically defined medium (CDM) supplemented with maltose or dextrin, expression of the MalR2 iModulon was significantly increased compared to CDM supplemented with glucose (Fig. 2A, bottom right) [6]. This finding indicates that carbon source availability strongly influences the transcriptional state of virulence genes, directly linking carbohydrate utilization to toxin regulation.

Hemolysis assays provided additional functional insights (Fig. 2B). In red blood cell lysis experiments, glucose supplementation supported hemolysis entirely dependent on the *slo* gene, which encodes streptolysin O (SLO). In contrast, maltose supplementation induced hemolysis exclusively mediated by streptolysin S (SLS). The *sagA* gene encodes the precursor peptide of SLS. Of note, dextrin supplementation triggered both SLS- and SLO-dependent hemolytic activities, producing a distinct outcome compared to maltose despite their structural similarity (Fig. 2A, bottom right; Fig. 2B) [6]. These observations highlight that dextrin utilization provides a unique regulatory cue, simultaneously activating both hemolysins. These results demonstrate that transcriptional induction of the *nga-ifs-slo* operon does not always correlate directly with dominance of specific hemolysins, underscoring the influence of post-transcriptional regulation and environmental factors on toxin expression.

Together, these findings reveal that the type of carbohydrate available to *S. pyogenes* profoundly alters both transcriptional regulation and functional toxin activity. In particular, dextrin utilization provides a unique regulatory cue that simultaneously promotes SLS- and SLO-mediated cytolysis, directly linking nutrient conditions to pathogenic potential.

5. Dextrin utilization contributes to the activation of CovRS-related iModulons

Dextrin utilization by *S. pyogenes* also influences the activity of key regulatory pathways beyond carbohydrate metabolism. Transcriptome-based iModulon analysis demonstrated that when the bacterium was cultured in CDM supplemented with dextrin, there was significant activation of CovRS-related iModulons (Fig. 2A, bottom right) [6]. CovRS is one of the most critical two-component regulatory systems in *S. pyogenes*, coordinating the expression of numerous virulence genes as well as pathways involved in metabolism, stress responses, and host adaptation. [9]. Specifically, dextrin supplementation increased the activity of both CovR-1 and CovR-2 iModulons relative to glucose conditions [6,18] (iModulonDB.org). In contrast, the maltose supplementation did not produce similar activation, highlighting dextrin's unique ability to potentiate CovRS-associated regulatory responses. Because CovRS is a master regulator that normally represses or fine-tunes virulence gene expression, the observation that dextrin activates CovRS-related iModulons suggests that this nutrient may serve as an environmental signal enhancing the pathogens capacity to adapt to host conditions. By engaging CovRS, dextrin utilization appears to promote a regulatory state that integrates metabolic inputs with virulence expression, thereby amplifying the pathogenic potential of *S. pyogenes*.

6. Dextrin-dependent growth enhancement may be driven by increased arginine metabolism

Growth assays demonstrated that *S. pyogenes* exhibits stronger proliferation when cultured in CDM supplemented with dextrin compared to glucose or maltose (Fig. 3, left) [6]. The underlying molecular mechanism for this growth advantage was initially unclear. To address the question, we performed transcriptomic profiling of bacteria cultured in CDM supplemented with different carbon sources. Dextrin utilization induced broad metabolic reprogramming, with a particularly striking upregulation of genes involved in amino acid metabolism, especially

arginine catabolism (Fig. 3, upper right) [19].

To test whether this transcriptional shift contributed to enhanced growth, we developed the first genome-scale metabolic model (GEM) of *S. pyogenes* serotype M1, designated iYH543 [19]. A GEM is a computational framework that comprehensively maps all known metabolic reactions of an organism, enabling *in silico* predictions of phenotypes under defined conditions. Using flux balance analysis (FBA), a mathematical architecture that optimizes flux distributions toward biomass production as a proxy for cellular growth, they evaluated how arginine uptake influenced cellular proliferation [20–22].

Simulation results revealed that even when uptake of other amino acids was restricted, incremental increases in arginine uptake flux led to proportional increases in predicted biomass yield (Fig. 3, bottom right) [19]. These results strongly support the hypothesis that dextrin-enhanced growth is at least partly attributable to increased capacity for arginine utilization. Together, these findings highlight a possible metabolic interplay between carbon source availability, amino acid metabolism, and bacterial growth, in which dextrin-dependent activation of arginine catabolism contributes to the observed growth advantage of *S. pyogenes*. This connection between nutrient availability and metabolic reprogramming may provide an additional layer of explanation for the pathogen's success during infection.

7. Current limitations in understanding dextrin-dependent pathogenic mechanisms

Despite important insights gained from recent systems biology approaches, the molecular mechanisms linking dextrin utilization to *S. pyogenes* pathogenicity remain incompletely defined. GEM and FBA have generated predictions that align with observed phenotypic differences, particularly the connection between dextrin and arginine metabolism. However, these computational inferences still require rigorous experimental validation *in vitro* and *in vivo*.

A major limitation is the current gap between transcriptional responses, model predictions, and direct mechanistic evidence. For example, while dextrin-dependent activation of virulence-associated iModulons and metabolic pathways has been demonstrated, the specific molecular signals that trigger these shifts remain unknown. Similarly, how dextrin-induced changes in central metabolism integrate with global regulators such as CovRS or Mga to fine-tune virulence gene expression is unresolved.

Future work will need to integrate transcriptomic and metabolomic data with targeted mutagenesis, biochemical assays, and infection models. Such studies will be essential to move beyond correlations and establish causality, clarifying how carbohydrate utilization directly influences both virulence programs and bacterial proliferation. Addressing these gaps will strengthen our mechanistic framework and reveal new opportunities for therapeutic intervention.

8. Conclusion

As a starch breakdown product, dextrin may also transiently appear in the pharynx, suggesting its potential physiological relevance as a nutrient source in one of the primary host niches of *S. pyogenes*. Dextrin utilization is emerging as an important determinant of both growth and virulence in *S. pyogenes*. Evidence from animal models demonstrates that the maltose/dextrin utilization operon contributes to bacterial fitness within host tissues and is co-activated with major toxins during necrotizing fasciitis. Dextrin further modulates hemolytic phenotypes by regulating the *nga-ifs-slo* operon, inducing both SLS- and SLO-dependent activities. In addition, dextrin uniquely activates CovRS-associated regulatory modules, linking carbohydrate availability to global reprogramming of virulence gene expression.

Beyond transcriptional regulation, dextrin enhances bacterial growth, at least in part through increased arginine metabolism, underscoring the importance of carbon–amino acid metabolic interplay in shaping pathogen physiology. Taken together, these findings position dextrin as a nutrient cue that integrates metabolic and regulatory pathways to enhance both the pathogenic potential and proliferative capacity of *S. pyogenes*.

A deeper understanding of how carbohydrate utilization drives the balance between growth and virulence will be critical for elucidating invasive infection pathophysiology. Future work that bridges metabolic modeling with experimental validation may also reveal novel therapeutic strategies to disrupt nutrient–virulence coupling in *S. pyogenes* and other invasive pathogens.

Ethical approval

This article does not involve studies with human participants or animals; therefore, ethical approval is not applicable.

Author contribution

Yujiro Hirose: Literature collection, figures, and drafted the manuscript.

Victor Nizet: The design of the review, assisted in writing, provided critical advice, and polished the content.

Shigetada Kawabata: The design of the review, assisted in writing, provided critical advice, and polished the content.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used ChatGPT 4.0 to assist with English-language editing. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

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Declaration of competing interest

The authors declare no conflict of interest.

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