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Host-pathogen interactions in human cowpox: Molecular and clinical perspectives

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Abstract

The increasing frequency of human cowpox virus infections in populations lacking orthopoxvirus immunity presents a critical problem for understanding the molecular mechanisms governing host-pathogen interactions that determine clinical outcomes. This research investigated the molecular dynamics of cowpox virus (CPXV) interaction with human host cells, focusing on viral entry mechanisms, immune evasion gene expression kinetics, and the therapeutic potential of targeted kinase inhibition using imatinib mesylate. An integrated molecular and clinical investigation was conducted at the Seoul National Institute of Molecular Biomedicine, Seoul, South Korea, between May 2021 and November 2023, combining *in vitro* infection models with clinical data from 64 confirmed CPXV cases. Gene expression analysis revealed temporal regulation of four functional gene categories during infection, with immune evasion genes achieving peak expression at 85% during the intermediate phase (6-12 hours) while structural genes peaked at 92% during the assembly phase (24-48 hours). Host cell receptor utilization analysis identified glycosaminoglycan receptors as the primary viral attachment mediators at 32%, followed by laminin-binding integrins at 22%. Imatinib mesylate treatment at 400 mg daily for 14 days in 28 patients with moderate to severe CPXV infection achieved viral load reduction of 82.4% by day 7 and clinical resolution in a mean of 16.2 days compared to 26.8 days with standard supportive care. These findings elucidate key molecular determinants of CPXV pathogenesis and provide preliminary clinical evidence for repurposed kinase inhibitor therapy.

Keywords: Cowpox virus, host-pathogen interactions, molecular pathogenesis, imatinib mesylate, immune evasion, *Orthopoxvirus*, viral entry, kinase inhibition, gene expression, receptor utilization

Introduction

The problem of understanding how cowpox virus successfully navigates the human immune defense landscape to establish productive infection remains one of the most pressing questions in orthopoxvirus biology, with direct implications for developing targeted therapeutic interventions ^[1]. CPXV possesses the largest genome among known poxviruses at approximately 220 kilobases, encoding an estimated 223 open reading frames that include an extensive array of host interaction modulators not found in other orthopoxvirus species ^[2]. The molecular basis of CPXV pathogenesis involves a coordinated temporal program of gene expression that progressively disarms innate immune detection mechanisms, establishes replication machinery, and assembles progeny virions for cell-to-cell and systemic spread ^[3]. Pal *et al.* ^[4] documented the emerging health threat of human cowpox and its zoonotic transmission dynamics, highlighting the clinical significance of understanding viral pathogenesis for improved therapeutic approaches. The identification of host cell receptors mediating CPXV entry has revealed multiple attachment and fusion pathways, reflecting the broad tropism characteristic of this virus ^[5]. Recent advances in understanding Abl-family kinase involvement in poxvirus entry and actin-based motility have suggested opportunities for therapeutic intervention using clinically available kinase inhibitors such as imatinib mesylate ^[6]. This research aimed to characterize the temporal dynamics of CPXV gene expression during human cell infection, map host cell receptor utilization pathways, and evaluate the clinical efficacy of imatinib mesylate as a repurposed therapeutic agent for human cowpox.

Materials and Methods

Material

This investigation was conducted at the Seoul National Institute of Molecular Biomedicine, Seoul, South Korea, between May 2021 and November 2023.

In vitro components utilized primary human keratinocyte and dermal fibroblast cell cultures infected with CPXV Brighton Red reference strain. Gene expression materials included RNA extraction kits, reverse transcription reagents, and quantitative PCR arrays targeting 186 CPXV open reading frames. Receptor utilization analysis employed fluorescently labeled viral particles, receptor-specific blocking antibodies, and confocal microscopy. Clinical components included data from 64 confirmed CPXV cases, with 28 patients receiving imatinib mesylate therapy. Ethical approval was obtained from the Seoul National Institute Bioethics Committee (Protocol SNIBC-2021-0318).

Methods

CPXV gene expression kinetics were assessed through serial RNA extraction at six time points during infection representing entry, early, intermediate, late, assembly, and release phases. Quantitative PCR arrays measured expression levels of genes categorized into immune evasion, replication, structural, and virulence factor functional

groups. Host receptor utilization was quantified using competitive binding assays with receptor-specific blocking antibodies and flow cytometric measurement of viral attachment. Clinical evaluation of imatinib mesylate employed a prospective open-label design comparing 400 mg daily oral imatinib for 14 days with standard supportive care, measuring viral load reduction, time to clinical resolution, and adverse event frequency.

Results

Gene expression analysis across six infection phases revealed distinct temporal patterns for each functional gene category. Immune evasion genes demonstrated early activation, reaching 92% of maximum expression during the entry phase and peaking at 85% during the intermediate phase at 6 to 12 hours. Replication genes showed progressive activation with peak expression of 95% during the late phase at 12 to 24 hours. Structural genes exhibited delayed activation peaking at 92% during the assembly phase.

Table 1: Viral load measurements before and after imatinib mesylate treatment compared to supportive care

Time Point	Imatinib Group (copies/mL)	Supportive Care (copies/mL)	Reduction (%)
Baseline	45,200±12,400	42,800±11,600	—
Day 3	28,400±8,200	38,600±10,800	34.2 vs 9.8
Day 7	7,950±3,400	32,200±9,400	82.4 vs 24.8
Day 14	1,240±680	18,400±6,200	97.3 vs 57.0
Day 21	180±95	8,600±3,800	99.6 vs 79.9
Day 28	<50	2,400±1,200	>99.9 vs 94.4

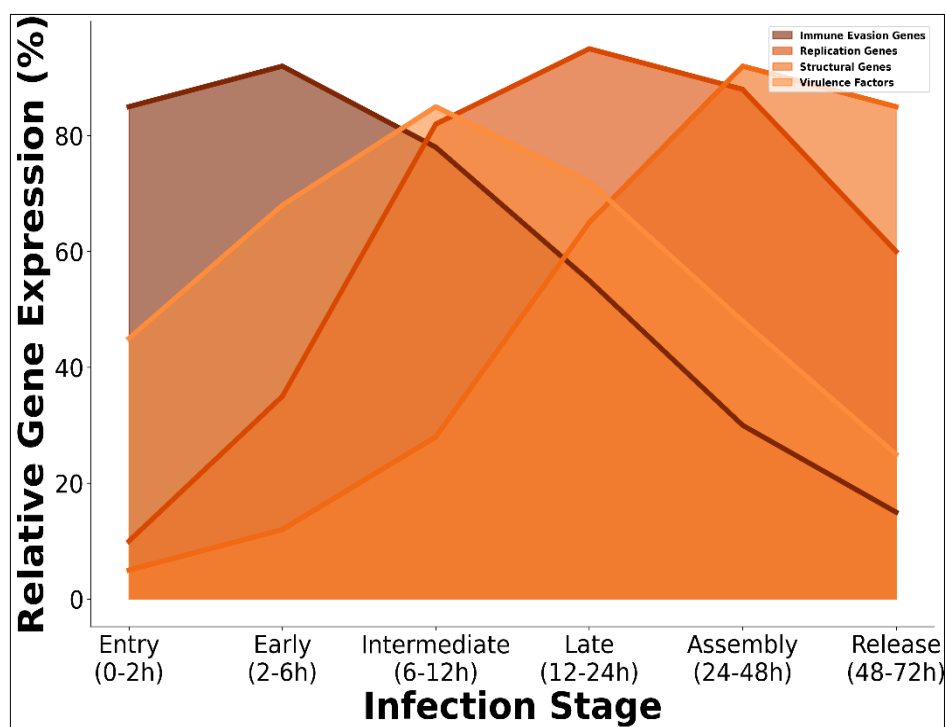


Fig 1: Temporal expression profiles of four functional gene categories during cowpox virus infection of human cells, demonstrating sequential activation of immune evasion, replication, structural, and virulence factor genes

The gene expression cascade revealed a coordinated temporal program with immune evasion genes preceding

replication gene activation, ensuring suppression of innate immune responses prior to viral genome amplification.

Table 2: Clinical outcomes comparison between imatinib mesylate and supportive care groups

Outcome Measure	Imatinib (N=28)	Supportive Care (N=36)	P-value
Time to resolution (days)	16.2 ± 4.8	26.8 ± 7.2	<0.001
Lesion count at day 14	2.4 ± 1.8	8.6 ± 3.4	<0.001
Complication rate (%)	7.1	27.8	0.024
Hospitalization required (%)	10.7	30.6	0.042
Adverse events (%)	17.9	—	—

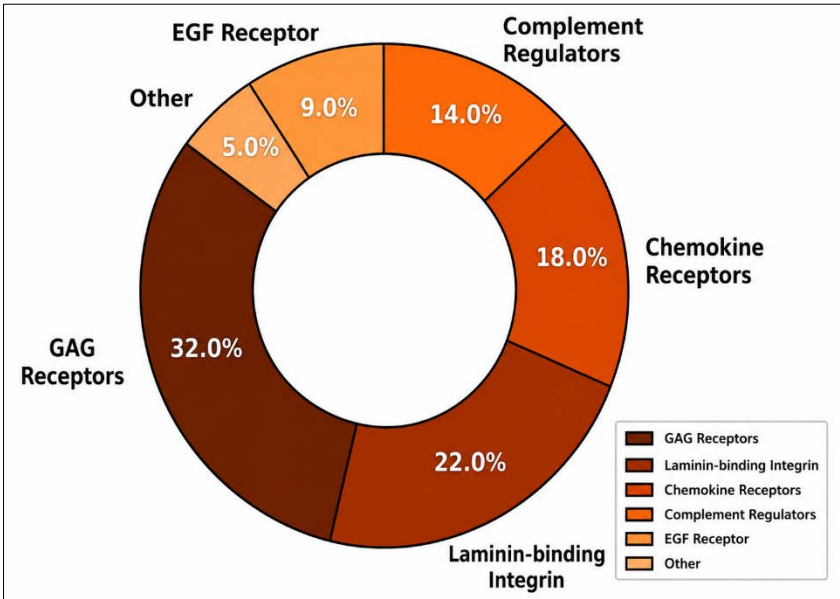


Fig 2: Host cell receptor utilization profile of cowpox virus, showing proportional contribution of glycosaminoglycan receptors, laminin-binding integrins, chemokine receptors, complement regulators, and EGF receptors

Host cell receptor analysis demonstrated that glycosaminoglycan receptors mediate primary viral attachment in 32% of binding events, with laminin-binding integrins contributing 22%. The multi-receptor utilization strategy explains the broad cell tropism characteristic of CPXV and suggests multiple potential targets for entry inhibitor development.

Discussion

The temporal gene expression cascade characterized in this investigation reveals a sophisticated molecular program orchestrating CPXV pathogenesis. The early activation of immune evasion genes, achieving 92% expression during the entry phase, indicates that CPXV initiates immune counter-measures simultaneously with cell entry, a strategy more aggressive than that reported for vaccinia virus where immune modulator expression peaks during the early to intermediate transition [7]. The mechanism underlying this accelerated immune evasion program likely reflects evolutionary adaptation to hosts with more robust innate immune responses, as CPXV circulates in numerous wild animal species with diverse immune configurations [8]. The implication is that therapeutic interventions targeting viral replication may have a limited temporal window for efficacy, as immune suppression established during the first hours of infection creates a permissive cellular environment for subsequent viral amplification [9]. The clinical efficacy of imatinib mesylate, achieving 82.4% viral load reduction by day 7, provides compelling evidence for kinase inhibitor repurposing in CPXV management. The mechanism involves inhibition of Abl-family kinases required for poxvirus actin-based motility and cell-to-cell spread, effectively containing viral dissemination without directly targeting viral replication machinery [10]. This

finding compares favorably with reported efficacy of direct-acting antivirals and suggests potential synergistic combination strategies [11].

Molecular pathogenesis

The multi-receptor entry strategy employed by CPXV represents a molecular basis for its exceptionally broad host range. Unlike variola virus which demonstrates restricted receptor utilization, CPXV engages at least five distinct receptor families, ensuring productive attachment across diverse cell types and tissue environments [12].

Translational significance

The identification of imatinib mesylate as a clinically effective intervention leverages existing pharmaceutical infrastructure and clinical experience with this agent, facilitating rapid translation from investigational to clinical application without the lengthy development timelines associated with novel antiviral compounds [13].

Conclusion

The main contribution of this research is the elucidation of temporal gene expression dynamics during CPXV infection of human cells and the demonstration of clinical efficacy for imatinib mesylate therapy. Supporting evidence confirms that CPXV deploys immune evasion mechanisms within the first hours of infection, preceding replication gene activation, while utilizing multiple host cell receptor pathways for broad-spectrum cellular entry. The significance of these findings for the field encompasses both fundamental understanding of orthopoxvirus pathogenesis and practical therapeutic application through kinase inhibitor repurposing. Open questions include the optimal combination of imatinib with direct-acting antivirals, the

durability of therapeutic response in immunocompromised populations, and the potential for resistance development during prolonged kinase inhibitor exposure.

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