DOI: 10.1002/hsr2.1732

LETTER TO THE EDITOR

Health Science Reports Open Access WILEY

Enhancing the use of natural killer cells as a promising therapy against monkeypox: Mechanisms and implications

Dear Editor,

We are writing to bring attention to the global rise in monkeypox (mpox) cases. The disease is similar to smallpox, but has a milder course and a lower mortality rate. However, its potential for human-to-human transmission and lack of specific antiviral treatments make it a pressing issue.

It is a zoonotic disease believed to have originated in rodents and primates, which serve as reservoir hosts. Transmission dynamics involve close contact with infected animals, body fluids, or contaminated surfaces. Therefore, individuals with occupational exposure to animals, such as hunters, veterinarians, and laboratory workers, are at higher risk of acquiring monkeypox. Studies have also shown the possible sexual transmission of the virus.[1] once the Monkeypox virus enters the human host, it encounters various barriers and immune responses. The initial interaction occurs at the site of infection, where the virus enters the monkeypox and is primarily transmitted to humans through direct contact with infected animals or their bodily fluids, as well as through respiratory droplets from infected individuals. Epithelial cells, such as those in the respiratory tract or skin, can support monkeypox virus replication.[2] the virus then spreads to regional lymph nodes, where they encounter immune cells, such as macrophages and dendritic cells. Recognition of the Virus by Innate immune cells, such as macrophages, dendritic cells, and natural killer (NK) cells, plays a crucial role in recognizing and responding to the monkeypox virus. They possess pattern recognition receptors, including toll-like receptors, which recognize specific viral components known as pathogen-associated molecular patterns (Figure 1). This recognition triggers the production of pro-inflammatory cytokines and

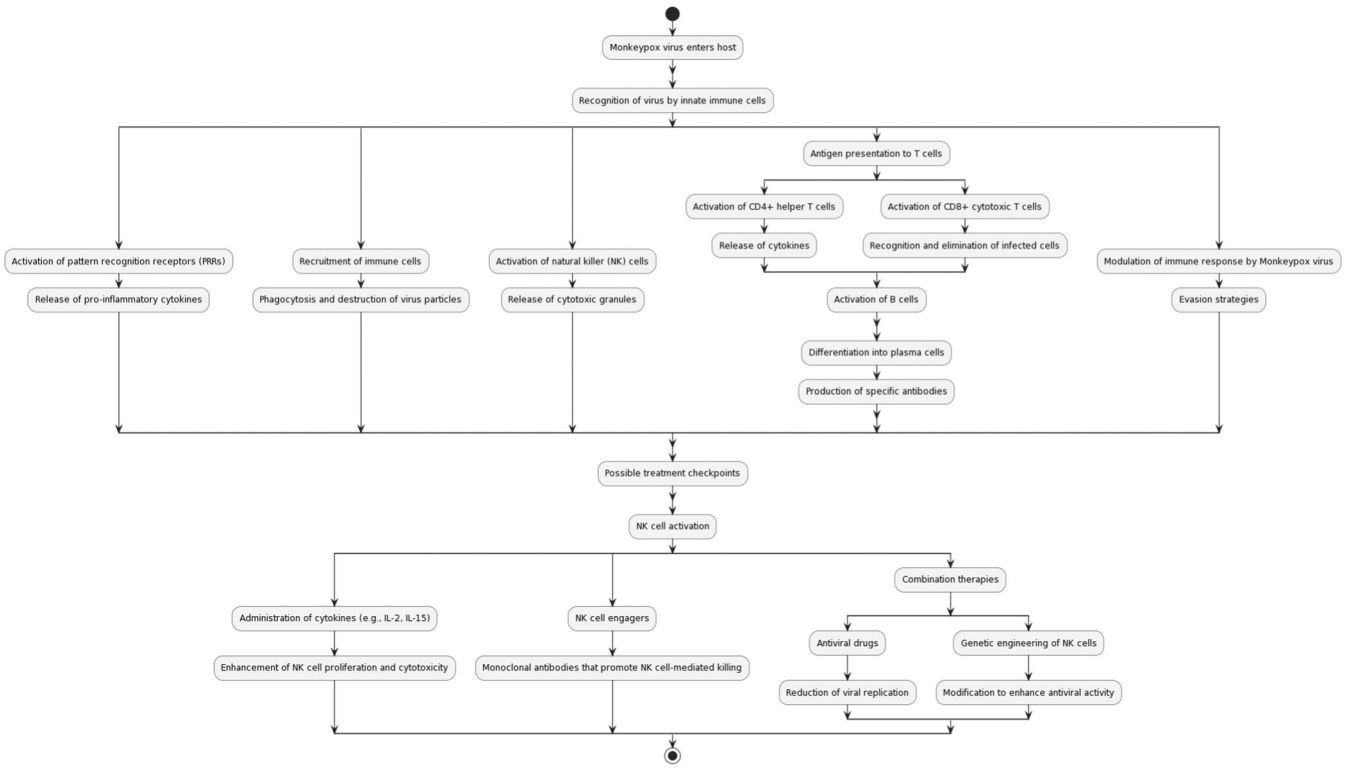

FIGURE 1 A flow diagram depicting the various host interactions and possible antiviral solutions to combat the spread of monkeypox virus.

chemokines, such as interferons (INFs), interleukin-1, and tumor necrosis factor-alpha.[3] A study by Song et al showed mpox inhibiting NK cells and preventing the formation of INFs.[4]

While the smallpox vaccine has been effective in prophylaxis, it only confers 85% protection against mpox,[5] antivirals were reported to be more effective as they decreased mortality and the number of cutaneous mpox lesions in the study done by Stittelaar et al.[6] Development of an antiviral in such case is necessary while we wait for a better vaccine with improved efficacy and specificity, one of the mechanisms we propose is to use NK cell stimulants or enhancers that are specific to almost all virus-infected cells, they can trigger the immune response in viruses such as human immunodeficiency virus, Cytomegalovirus and SARS-CoV-2.[7,8] and antagonize the viral particle by direct inhibition or by the production of a monoclonal antibody, which directly causes activation of more NK cells and in turn boosts the T-cell-mediated cytotoxic effects. Resistance to NK cells by the mpox virus increases its lethality, which proves their importance in the successful clearance of the virus and the need to develop antiviral agents, as further theorized in an article by Fang et al.,[9] Immunotherapy targeted to the NK cell receptor NKG2D is essential for killing mpox-infected cells, as highlighted in the review study conducted by Li et al.[10]

Understanding intricate host interactions during monkeypox infection is crucial for developing effective vaccines and antiviral therapies. By targeting specific components of the immune response or viral proteins involved in host interactions, researchers can develop interventions that enhance immune recognition, promote viral clearance, and prevent severe disease.

AUTHOR CONTRIBUTIONS

Kahan Mehta: Conceptualization; Investigation; Visualization; Writing—original draft; Writing—review and editing. **Maruya Joshi**: Data curation; Formal analysis; Writing—original draft; Writing—review and editing. **Jugal Bhatt**: Investigation; Writing—original draft; Writing—review and editing. **Nency Kagathra**: Investigation; Writing—original draft; Writing—review and editing. **Mohamed Omar**: Supervision; Validation.

ACKNOWLEDGMENTS

No funding was obtained for this study.

CONFLICT OF INTEREST STATEMENT

The author declares no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study, all data underlying the results presented are available in the article.

ETHICS STATEMENT

The authors have nothing to report.

Kahan Mehta[1]
Maruya Joshi[1]
Jugal Bhatt[1]
Nency Kagathra[2]
Mohamed Omar[3]

[1]*Department of Internal Medicine, GMERS Medical College and Hospital, Vadodara, India*
[2]*Department of Medicine, Zydus Medical College, Dahod, India*
[3]*Faculty of Health Sciences, University of Nairobi, Nairobi, Kenya*

Correspondence
Kahan Mehta, Department of Internal Medicine, GMERS Medical College and Hospital, Vadodara, India.
Email: research.kahan@gmail.com

Mohamed Omar, Faculty of Health Sciences, University Way, 00100 Nairobi, Kenya.
Email: mohabhullah13@gmail.com

ORCID

Kahan Mehta https://orcid.org/0000-0003-3926-6175
Mohamed Omar http://orcid.org/0009-0001-9353-8015

REFERENCES

1. Ciccarese G, Di Biagio A, Bruzzone B, et al. Monkeypox outbreak in genoa, Italy: clinical, laboratory, histopathologic features, management, and outcome of the infected patients. *J Med Virol*. 2023;95(2):e28560. doi:10.1002/jmv.28560
2. World Health OrganizationMonkeypox. https://www.who.int/news-room/fact-sheets/detail/monkeypox; 2023.
3. Lum FM, Torres-Ruesta A, Tay MZ, et al. Monkeypox: disease epidemiology, host immunity and clinical interventions. *Nat Rev Immunol*. 2022;22(10):597-613. doi:10.1038/s41577-022-00775-4
4. Song H, Josleyn N, Janosko K, et al. Monkeypox virus infection of rhesus macaques induces massive expansion of natural killer cells but suppresses natural killer cell functions. *PLoS One*. 2013;8(10):e77804. doi:10.1371/journal.pone.0077804
5. World Health Organization. Mpox (monkeypox) outbreak: global trends; 2022. Available from: https://worldhealthorg.shinyapps.io/mpx_global/
6. Stittelaar KJ, Neyts J, Naesens L, et al. Antiviral treatment is more effective than smallpox vaccination upon lethal monkeypox virus infection. *Nature*. 2006;439(7077):745-748. doi:10.1038/nature04295
7. Arase H, Mocarski ES, Campbell AE, Hill AB, Lanier LL. Direct recognition of cytomegalovirus by activating and inhibitory NK cell receptors. *Science*. 2002;296(5571):1323-1326. doi:10.1126/science.1070884
8. Market M, Angka L, Martel AB, et al. Flattening the COVID-19 curve with natural killer cell based immunotherapies. *Front Immunol*. 2020;11:1512. doi:10.3389/fimmu.2020.01512
9. Fang M, Lanier LL, Sigal LJ. A role for NKG2D in NK cell-mediated resistance to poxvirus disease. *PLoS Pathog*. 2008;4(2):e30. doi:10.1371/journal.ppat.0040030
10. Li H, Huang QZ, Zhang H, et al. The land-scape of immune response to monkeypox virus. *EBioMedicine*. 2023;87:104424. doi:10.1016/j.ebiom.2022.104424