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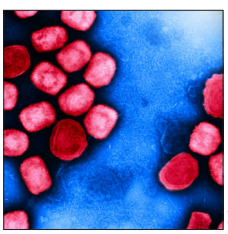
Monkeypox infection creates immune signatures of disease progression



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As of Oct 28, 2022, the ongoing monkeypox pandemic has resulted in more than 76 806 cases worldwide. This is the largest outbreak of monkeypox virus outside of western and central Africa and is a clear indication that the world needs to pay more attention to this disease. The sporadic nature of the outbreaks, combined with the small size and limited number of cases, has hampered systematic investigation into the host response to infection with this orthopoxvirus.

The current outbreak is notable in that the vast majority of the cases are occurring in men who have sex with men. This community has a number of other prevalent conditions, including HIV positivity, immunosuppression, and other sexually transmitted diseases. This community also has in some cases highly connected sexual networks that might facilitate the spread of the disease. Collectively, these characteristics have resulted in a dramatically different clinical presentation than the historic norm for monkeypox infection, which was a barrier to accurate identification of the pathogen in many of the cases observed early in the pandemic.[1,2] The effect of rapid and continual monkeypox transmission in a community with these characteristics has not yet been determined but is likely to have a powerful effect on the course of the pandemic. These characteristics also need to be taken into consideration during vaccination efforts and plans for non-pharmaceutical interventions to assist in outbreak control strategies.[3] We need updated clinical and diagnostic guidance clearly communicated to health-care providers, and expanded testing to include those patients who might not present with typical monkeypox symptoms. Expanded access to vaccination will also be a crucial element of outbreak control. The development of predictive biomarkers will also enable us to better provide targeted clinical care (eg, antivirals to those likely to develop severe disease). Many of these action items are already being implemented.

The vast majority of the information known about orthopoxvirus infections comes from historical data collected before smallpox was eradicated and from studies involving vaccinia virus. Monkeypox infections have been studied in both humans and animals, and we have already seen large differences in the clinical picture and epidemiology of this disease during the current pandemic.[4] How the body responds to monkeypox infection as opposed to other orthopoxviruses[5] is a crucial knowledge gap that needs to be addressed to respond effectively to the current pandemic. Equally crucial is contemporary human data documenting the effectiveness of smallpox or monkeypox vaccination against monkeypox infection.

In *The Lancet Infectious Diseases*, Chiara Agrati and colleagues[6] provide insights into the immune response to monkeypox infection in a cohort of 17 patients with laboratory-confirmed monkeypox infection with a set of ten healthy donors used for comparison purposes. Longitudinal samples were available for a subset of the cohort, allowing the investigators to evaluate changes in immunologic parameters over time. In this study, investigators focused on several immune outcomes: T-cell phenotype was assessed by flow cytometry; antigen-specific T-cell responses were assessed by standard interferon-γ ELISPOT using peptide pools covering the sequence of three viral proteins (MVA074R, MVA105L, and MVA121L); and cytokine concentrations in plasma were quantified using ELLA.

The study found that there was an early increase in the frequency of CD8+ T cells with decreased CD4+ T cell numbers in patients with monkeypox. Both types of T cells exhibited an increase in effector phenotype cells and cells expressing the CD38 activation marker. These changes normalised 12–20 days after symptom onset. The changes in T-cell phenotype corresponded with an increase in inflammatory cytokine concentrations (interleukin [IL]-1b, IL-6, IL-8, and tumour necrosis factor) in plasma samples. With regards to antigen-specific T-cell responses, all but one patient had detectable (Th1-biased) poxvirus-specific T cells. Interestingly, the few patients with less severe symptoms also exhibited a blunted cytokine response; however, this finding would need to be verified in a larger cohort.

Only one of the study's patients had a smallpox vaccine history; therefore, the investigators could not evaluate the effect of pre-existing immunity on the

noted immunologic changes. With regards to HIV, seven of the 16 patients were HIV positive (all had CD4 counts above 400 cells per µL) and no major differences were noted in the monkeypox infection-induced immunologic perturbations between HIV-negative and HIV-positive cases.

In summary, there is an early and powerful T-cell response to monkeypox infection, characterised by elevated inflammatory mediators. Similar to what has been observed with other orthopoxvirus infections, the T-cell response is Th1 biased.[7] This study was not able to evaluate responses beyond about 20 days, but reports from the 2003 monkeypox outbreak in the midwestern USA indicate that T-cell responses last for at least 1 year following infection and mirror data from smallpox infection and vaccination studies showing durable T and B cell responses lasting for decades.[8,9]

This study has several limitations, including a small sample size (n=17), a narrow geographical range (Rome, Italy), and a limited set of immunologic markers (cytokine secretion, immune cell phenotypes, and T cell responses to only three viral proteins). Although an important initial step in determining molecular signatures of infection, ideally follow-up studies will evaluate these markers in additional cohorts (broadening the applicability of the results) and expand the assessment to include more immunologic markers (both innate and adaptive).

This monkeypox outbreak is different from every previous monkeypox outbreak. Several factors are likely to contribute to this difference, including: genetic differences in the circulating strains, differences in underlying health of the affected populations, differences in access to health care and effective treatments, and pre-existing immunity in the affected communities. The development of immunologic signatures, especially if they can be linked to clinical disease course, response to treatment, or even disease susceptibility, would provide a powerful tool for treatment and disease management, and would inform effective use of existing vaccines.

I am the inventor on patents held by Mayo Clinic for the identification of vaccinia virus-derived immunogenic epitopes and peptide-based vaccines for smallpox. I have report having served as a consultant for Sanofi and Merck, and I have received royalties from ICW Ventures for the development of a COVID-19 vaccine.

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