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Editorial

Host-directed therapies: old and new approaches for the treatment of infections

Infectious diseases remain a leading global cause of morbidity and mortality [1]. Even in rich countries with health services and antibiotics availability, respiratory tract infections are a major cause of death [1]. In addition, the treatment or prevention of infection is vital for high-quality maternal and child health, management of immunosuppressed patients, and many surgical procedures.

In the last 20 years, zoonotic diseases have been responsible for important outbreaks such as Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), Zika infection, Mpox Disease, and of course, the pandemic due to COVID-19 resulting in severe morbidity and deaths of millions of people. There is an urgent need for new treatment options.

The development of antimicrobial resistance (AMR) undermines the ability to prevent and treat with antimicrobials (such as antibiotics, antivirals, antifungals, and anti-parasitic drugs), resulting in challenging infections with poor outcomes and increased mortality. Further compounding the issue is the transmissibility of AMR with the risk of spread to the local community and beyond. AMR is a serious health problem, directly responsible for 1.27 million global deaths in 2019 and indirectly contributing to 4.95 million deaths [2].

In the field of infectious diseases, in addition to targeting the pathogen itself, it is crucial to understand the interaction between the host and the pathogen and to define the mechanisms of pathogenesis. Such knowledge will be important to the development of new therapeutic approaches which could potentially improve clinical outcomes. Today, there is a renewed interest in host-directed therapies (HDTs), defined as host-directed interventions that modify intracellular pathways of innate or adaptive immune responses to microbes to augment immune response and/or to decrease immunopathology [3]. In the past, HDTs have likely been in use inadvertently; for example, para-aminosalicylic acid (PAS) in tuberculosis may have more impact on signaling paths than on *M. tuberculosis* killing [4].

HDTs represent a good strategic approach to combat drug-resistant pathogens. It has been shown that almost 90% of HDTs evaluated had similar activity against drug resistance and drug-sensitive pathogens [5]. In addition, HDTs are hypothesized to decrease the chance of developing drug resistance, particularly because it is thought that HDTs target multiple cellular and intracellular mechanisms essential for microbial replication and pathogenesis. Therefore, in these conditions, the generation of resistance would require complex actions that are unlikely to occur concomitantly [5].

HDTs are expected to enhance the anti-microbial treatment effects and may work across different pathogen species. It has been shown that among the 183 host-directed drugs evaluated in a recent study [5], 55 (30%) had activity against more than one pathogen; they target mainly close evolutionary family members (29 compounds, 52%), although 48% showed a cross-species activity against evolutionary distinct families, kingdoms, and domains.

HDTs include drugs with a variety of mechanisms of action (Figure 1). Among HDTs augmenting host immunity, there are cell-based compounds such as CAR-T cells for people living with HIV, leading to a transient HIV-1 viral reservoir reduction [6], cytokines such as type I interferon (IFN) treatment for chronic Hepatitis C (HCV) or COVID-19 [7–9], anti-oxidants such as N-acetylcysteine protecting cells from oxidative damage in tuberculosis [10], passive infusion of anti-pathogen antibodies (used for COVID-19 [11] and respiratory syncytial virus infection (RSV) [12]), macrophage-targeting strategies (as in tuberculosis [13]) and prevention with vaccination.

Among the HDTs that reduce immunopathology by suppressing inflammation generated by the immune response towards the pathogen, there are compounds targeting cytokines including anti-cytokine antibodies (such as Interleukin (IL)-6 receptor blockade in COVID-19 [14]); tumor necrosis factor (TNF) treatment of paradoxical reactions to antimycobacterial therapy in tuberculous meningitis [15]; cytokine and chemokines modulators (such as Janus kinase (JAK) inhibitors in COVID-19 [14]; corticosteroids in COVID-19 [14] or in tuberculosis meningitis [16]); anti-oxidants such as N-acetylcysteine in tuberculosis [10], vitamins such as Vitamin D which showed an effect in reducing inflammation in pulmonary tuberculosis [17], anti-inflammatory drugs (like statins and cyclooxygenase 2 inhibitors in tuberculosis [18,19]) and inhibitors of the enzymes damaging the tissues such as the inhibitors of the matrix metalloproteinase (MMPs) [20,21].

HDTs are potential therapeutics when drugs against pathogens are unavailable, exemplified by COVID-19 for which corticosteroids and drugs against cytokines have been crucial to decrease mechanical ventilation and reduce mortality [14]. Spurred by the remarkable successes of cancer immunotherapies, their adoption into infectious diseases clinical practice should be key. Just as immunotherapy has transformed oncology therapy [22], HDTs can widen the drug armamentarium to treat infections by reducing tis-

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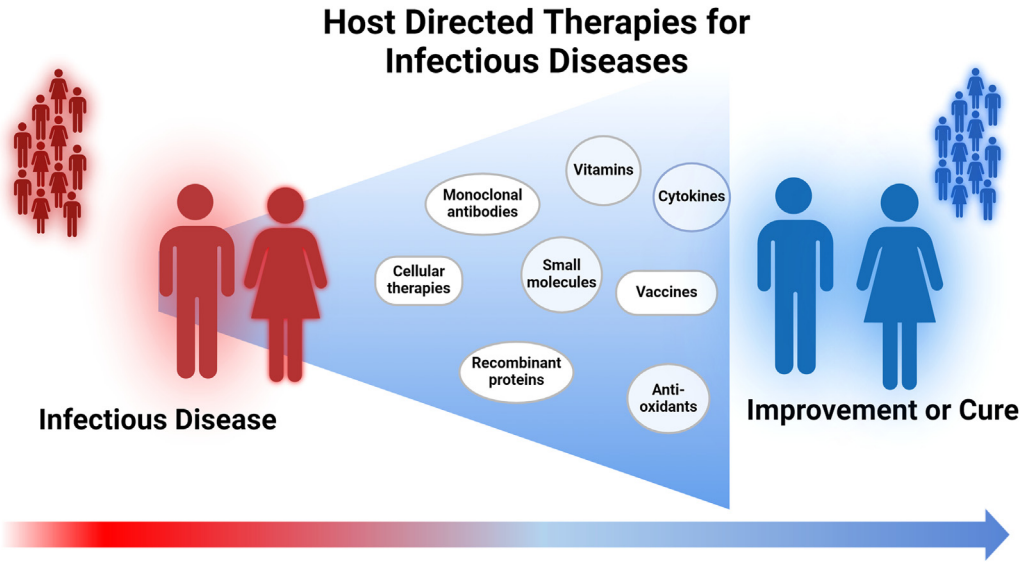

Figure 1. Different compounds can be used for host-directed therapies in infectious diseases. (figure created with BioRender.com)

sue damage (such as in COVID-19 or tuberculosis), preventing functional impairment – such as liver dysfunction in hepatitis B Virus (HBV), and improving long-term survival.

There is an urgent need for new HDTs and research to test the efficacy of the existing compounds in fully powered and late-phase clinical trials. Once their efficacy is demonstrated, HDTs may help address the gaps in infectious disease treatment, and lead to decreased AMR, reduced treatment duration, and decreased pathogen transmission to the community with improved clinical outcomes.

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