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Supplementary webappendix

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ONLINE SUPPLEMENTAL APPENDIX

Title:

Advancing Host-Directed Therapies for Infectious Diseases – Current Status, Recent Progress and Future Prospects

Authors:

Alimuddin Zumla, Martin Rao, Robert S Wallis, Stefan Kaufmann, Roxana Rustomjee, Peter Mwaba, Cris Vilaplana, Dorothy Yeboah-Manu, Jeremiah Chakaya, Giuseppe Ippolito, Esam Azhar, Michael Hoelscher, Markus Maeurer* for the Host-Directed Therapies network consortium

1. HDT for bacterial sepsis.

Sepsis is regarded as the most common cause of death among new-borns globally, with at least 500, 000 deaths reported on an annual basis (1). Gram-negative bacteria i.e. staphylococci, enterococci, *Klebsiella sp*., *Escherichia coli*, *Neisseria sp.*, pseudomonads are most frequently associated with infant deaths due to sepsis, up to 92% of cases in several clinical studies reported to date (2). Mortality due to sepsis is largely due to aberrant immune reactions in the patient (collectively known as systemic inflammatory response syndrome, SIRS – which results in septic shock), marked by an interplay of pro- and anti-inflammatory host factors, in combination with cellular exhaustion (3, 4). At present, the clinical management of sepsis relies on antibiotics, largely comprising ampicillin or penicillin in combination with gentamicin for infants below the age of 2 months. For infants older than 2 months, benzylpenicillin plus chloramphenicol is used. In clinical cases suspected of sepsis due to staphylococcal infection, a combination of flucloxacilin and third-generation antibiotics is administered, although the latter has become the mainstay of treatment in many developing countries due to its low cost (2, 4). Third-generation cephalosporins are also used in drug-resistant infections causing sepsis; however, resistance to all types of chemotherapeutic agents in current clinical practice for sepsis treatment have been frequently reported (2).

Host-directed clinical measures have been attempted as adjuncts to standard antibiotic therapy for sepsis management in the clinic. Ibuprofen therapy, although successful in reducing pyrogenicity in patients with sepsis by downregulating thromboxane and prostaglandin production, did not result in improved survival (5). High levels of IL-6 and IL-10 have been detected in sera of patients with SIRS, concomitant with severity of sepsis and disease (6). Prior use of atorvastatin by patients with sepsis manifested in lower baseline levels of serum IL-6, concomitant with shorter hospital stays and better survival (7). A randomized controlled trial in 100 statin-naive patients who were hospitalized with sepsis showed that inpatient atorvastatin (40 mg per day) reduced progression to severe sepsis by 83% (24% in control patients vs 4% in treated patients; P = .007) (8).

In an extensive review of anti-TNF-α treatment of patients with septic shock, a trend towards improved survival was noticed among patients with high levels of circulating IL-6, in addition to reflecting a general reduction in 28-day overall (all-cause) mortality (9). Blockade of IL-1 receptor with recombinant human IL-1R antagonist (anakinra) did not result in a significant improvement of 28-day all-cause mortality in

patients with severe sepsis (10). Newer strategies aimed at reducing mortality have focussed on modulation of host physiological pathways involved in secretion of inflammatory cytokines (pharmacological reduction of IL-1β using glyburide)(11, 12) cholesterol metabolism (administering recombinant high-density lipoprotein)(13) and T-cell exhaustion (targeting the PD-1/PD-L1 pathway using recombinant antibodies) (14, 15).

2. Targeting potential host factors for clinical development of host-directed therapy against infectious disease.

Sialic acid-containing host cell receptors

Sialic acid is a glycan residue that is ubiquitous in biological systems. In mammals, sialic acid is an integral component of several cellular receptors, participating in general physiology and homeostasis (16). Influenza virus easily targets host cells expressing sialic acid-containing receptors for entry and replication. Cleavage of this motif using sialidase-based agents i.e. DAS181 would contribute to dramatic reduction in viral load (17). Besides influenza, a myriad of other pathogens including and not limited to *Vibrio cholerae*, *Clostridium tetani*, MERS-CoV and *H. pylori* also use sialic acid-containing receptors to initiate pathogenesis in humans – either for cell entry, toxin uptake or immune suppression (16). These receptors therefore present a highly attractive target for host-directed therapy. One such receptor, DPP4 (host receptor for MERS-CoV entry) has already been discussed earlier in this review, and is the target of the currently used anti-diabetic drugs sitagliptin and vildagliptin (18).

MAP kinase

Mitogen-activated protein kinases (MAPK) are key enzymes that participate in crucial biochemical processes of eukaryotic cells, ranging from cell proliferation to apoptosis. Among the various MAPK enzymes in existence, the p38 MAPK is of particular importance to infection biology owing to its involvement in cytokine signalling (including TNF-α and IL-1β), apoptosis and autophagy (19). Several host-directed interventions targeting (both inhibition and activation) p38 MAPK have been reported for various infectious diseases.

Ebola virus: Inhibition of p38 MAPK with experimental pyridinyl imidazole compounds i.e. SB203580 and SB202190 abolished Ebola virus entry and thus, replication in primary human dendritic cells (DCs) (20). This was concomitant with reduced production of pro-inflammatory cytokines including TNF-α, IL-12, CXCL10 and RANTES.

Dengue virus: DENV-induced secretion of pro-inflammatory mediators such as TNF-α, IL-8 and CCL5 by infected myeloid-derived cells were shown to be downregulated via pharmacological inhibition of p38 MAPK with the experimental drug SB203580 (21). Furthermore, mice which were first infected with DENV and then treated with an experimental p38 MAPK inhibitor exhibited reduced vasculopathy and intestinal haemorrhage.

Enterovirus: p38 MAPK was also shown to induce TNF-a and IL-6 in DCs infected with enterovirus 71, and can be pharmacologically abrogated with SB203580 treatment (22).

Influenza virus: Inhibition of p38 MAPK with SB202190 shown to protect mice from lethal infection with H5N1 or H7N7 avian influenza A virus infection via dampening of pro-inflammatory cytokine production ultimately manifesting in extension of survival (23).

Tuberculosis: In TB*,* suppression of IFN-γ production by CD4 T cells has been shown to be a direct effect of *M. tb* ESAT-6-mediated p38 MAPK upregulation (24). Pharmacological inhibition of p38 MAPK activity with SB203580 helped restore the ability of T cells to secrete IFN-γ in response to antigenic stimulation. It was later shown that pharmacological blockade of EGFR using gefitinib concomitantly abolished p38 MAPK activity in *M. tb*-infected cells, consequently killing intracellular bacteria via autophagy. Subsequent preclinical validation of this phenotype resulted in reduced *M. tb* proliferation in the lungs of infected mice (25). MAPK inhibition could therefore be a viable strategy to control excessive inflammation and tissue destruction during the course of progressive TB disease.

Blastocystis: Infection with the protozoan parasite *Blastocystis sp.* infection has been implicated in the pathogenesis of inflammatory bowel diseases in humans. In a murine model of primary *Blastocystis* infection, induction of MAPK expression by the pathogen was shown to trigger release of pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α (26). Pharmacological inhibition of p38 MAPK with SB203580 resulted in reduced production of particularly IL-6, highlighting the central role played by this enzyme in disease progression.

Aryl hydrocarbon receptor

The aryl hydrocarbon receptor (AhR) has long been known as a host molecule which detects and responds to environmental toxins such as the polycyclic dioxins (27). Its newly-described role as a pathogen recognition receptor, with affinity for pigmented moieties seems to play important protective roles in infection with *Pseudomonas aeruginosa* and *M. tb* (28), *Plasmodium berghei* (29) and *Listeria monocytogenes* (30) – the majority of which are intracellular pathogens. Perhaps activation of AhR in latent infections / for prophylaxis using dioxin-like particles that are nonetheless non-pathological might be of clinical benefit? At the same time, it is important to ascertain that biological processes that induce production of kynurenines are not upregulated since this may be oncogenic, in an AhR-dependent manner (31).

Complement pathway

The complement pathway represents a highly important arm of innate immune responses, thus constituting a crucial defence mechanism against intracellular and extracellular pathogens. In clinical assessment of antibacterial vaccines and biologicals, serum bactericidal assays (SBAs) are used to gauge antigen-specific complement-dependent killing of pathogenic bacteria (32). Although the use of complement proteins themselves is not host-directed, administration of the antibody-binding complement protein C1q to patients may enhanced pathogenic-specific antibody activity to control infection and disease, at large. Nevertheless, a novel therapeutic peptide (EP67) derived from the C-terminal of the C5a complement protein (involved in formation of the membrane attack complex on the surface of bacteria) was evaluated against Group B Streptococcus (GBS) and methicillin-resistant *Staphylococcus aureus* (MRSA) infections in mice (mouse model of dermonecrosis). Treatment with EP67 appeared to reduce GBS load in the vaginal tract, showing a direct bactericidal effect against the cocci (33). In MRSA-infected mice, subcutaneous EP67 treatment resulted in reduction of skin lesion size and bacterial load coupled with increased neutrophil infiltration to ameliorate disease (34).

Sphingosine-1-phosphate

Sphingosine-1-phosphate (S1P) is a vital lipid mediator circulating mainly in blood. It is biosynthesised via the enzymatic activity of sphingosine kinase 1 (SK1) signals via the S1PR1, and has implications on a variety of biological processes including lymphocyte trafficking, cholesterol metabolism and angiogenesis among others (35). Importantly, activation of the S1P pathway may improve egress of antigen-specific T and B cells from lymphatic compartments into tissue to control infection (36, 37).

A recently published study revealed that pharmacological induction of S1P release during active murine infection with *Bordetella pertussis* resulted in decreased lung tissue pathology accompanied by reduction in bacterial load (38). It has also been shown in a mouse model of *Cryptococcus neoformans* infection that addition of exogenous S1P to mice deficient for SK1 promoted early neutrophil influx into the lungs and contributed to the formation of host-protective granulomas (39), which might also be relevant in prevention of MRSA-induced dermanecrosis (34).

tRNA synthesis

Transfer RNA (tRNA) is crucial for transporting newly synthesised single-stranded mRNA to ribosomes for translation into proteins. Irreversible abrogation of this process may effectively lead to cell death. Targeting tRNA synthetase has been discussed as a potential target for directed therapy, both in prokaryotes and eukaryotes. Initial studies using borrelidin, a polyketide derived from *Streptomyces sp*. (40) capable of selectively inhibiting the activity of threonyl tRNA synthetase in *P. falciparum* (41), *T. brucei* (42) as well as acute lymphoblastic leukaemia cells (43) have further validated blockade of tRNA synthesis as a very promising druggable target for clinical translation.

Neuropilin-1

Neuropilin-1 (NRP1) is a transmembrane co-receptor that binds to various receptor tyrosine kinases such as vascular endothelial growth factor receptor (VEGFR), transforming growth factor beta receptor (TGF-βR) and plexins (44). As such, VEGF, semaphorins, TGF-β1 and heparin glycans can bind to the NRP1 receptor complex to initiate the signalling cascades that promote angiogenesis, neural system development and cell adhesion (44). NRP1 can also be shed from cells, and is thus detectable in serum (45). Although NRP1 is strongly associated with regulatory T cells (Tregs) in mice, it is rather a marker for activated human T cells, in addition to its absence on human Tregs (46). NRP1 expression is reflective of poor prognosis in lung, prostate, colon, pancreatic and breast cancer, which led to its development as a therapeutic target (47). The inaugural clinical trial with anti-NRP1 mAb (MNRP1685A) against advanced solid tumours (including lung, pancreatic and CRC) was published in 2014, displaying a good safety profile in patients (48). Co-administration of MNRP1685A and bevacizumab (anti-VEGF) has also been clinically investigated in patients with advanced solid tumours, but reconsideration of the standard bevacizumab dose is required, if given in combination with MNRP685A (49). Pertaining to infectious diseases, NRP1 has been associated with promotion of liver cirrhosis in patients with HCV infection (50), enhancement of EBV entry into human nasopharyngeal epithelial cells (51) as well as HTLV-driven syncytia formation in human T cells (52). These findings warrant further investigation of NRP1 as an HDT target in human infectious diseases.

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