Immunomodulatory Effect of Amphotericin B Enhances Antiviral Activity

Dear Editor,

Amphotericin B (AmB), which belongs to the polyene group of antibiotics, has a wide spectrum *in vitro* and *in vivo* antimicrobial activity against fungi and parasites, and resistance to AmB is rare despite extensive use.[1] Recently, some studies focused on the potential antimicrobial action of AmB against some enveloped and nonenveloped viruses. Besides AmB's utilization as an antimicrobial agent to treat fungi and parasites, AmB and its derivatives against viral infection have been evaluated, enhancing the phenomena of antiviral activity of AmB toward numerous viruses by different mechanisms of actions. Some searches studied the efficacy of AmB to treat human immunodeficiency virus, Japanese Encephalitis Virus, and the Rubella virus.[2]

Nearly 5000 species of viruses have been identified in detail, of the millions of virus types in the world. Viruses are considered the most numerous type of biological entity, and they are found in almost every ecosystem on Earth.[3] It is difficult to treat viral infections, and some viruses have no specific therapy.

AmB destroys fungi and single-cell protozoa such as *Leishmania* spp. by preferentially binding to ergosterol than cholesterol because of its high affinity toward ergosterol. Another mechanism is by the production of free radicals inside fungi that cause oxygen depletion.[1] Because it has immunomodulatory effects, it is capable of inducing pro-inflammatory mediators.[4]

Toll-like receptor (TLR)-2 (TLR2) and CD14 have demanded AmB-dependent inflammatory stimulation of innate immune responses, as well as TLR4 may also provide stimulation. AmB produces a transcription of inflammatory cytokines such as interleukin (IL)-6, tumor necrosis factor-alpha (TNF-α), and IL-1β, besides chemokines (IL-8, monocyte chemoattractant protein-1, and MIP-1β), nitric oxide, prostaglandins, and intercellular adhesion molecule-1 from murine and human innate immune cells *in vitro*.[5]

It has potent immunomodulatory properties on the host cells *in vitro* and *in vivo,* enhancing the immune response of the host. This effect of AmB is not only in the presence of the pathogen, but also when the causative agent is absent by stimulating the production of multiple mediators of the immune system.[4] However, mechanisms by which AmB activates the immune system are still not fully understood.

AmB increases interferon production in mouse L929 cells treated with it, by enhancing the penetration of polyriboinosinic-polyribocytidylic acid of the cell membrane that acts as a trigger to interferon production. Interferon titers were enhanced significantly by AmB at 5 μg/ml and increased almost 10-fold at 25 g/ml. AmB and its derivatives can produce pro-inflammatory cytokines by interfering with the macrophage activation state. It increases TNF-α production that leads to the synthesis of superoxide dismutase, which produces the substrate of catalase such as hydrogen peroxide.[6]

Although AmB is capable of inhibiting fungal growth by direct killing mechanisms, it is considered to directly activate the host's innate immunity, it has been reported to trigger IL-1β secretion in monocytes, and also it induces potassium efflux from the cells that lead to increasing IL-1β secretion. The adjuvantic efficacy of AmB is applicable, safe, and effective for human vaccines at a dose of 100 μg.[5]

It can bind TLRs (TLR2 and TLR4), which results in the release of cytokines/chemokines and pro-inflammatory and anti-inflammatory mediators.[4] The defensive effects during infection were correlated with the immunomodulatory properties and the pro inflmmatory activity caused by AmB that enhances the antifungal activity of polymorphonuclear cells and pulmonary alveolar macrophages against conidia and/or hyphal phase of *Aspergillus fumigatus*.[6]

For rubella viruses, AmB revealed an antiviral impact at the late stage of virus replication; also AmB interacts with the viral envelope at the early stage of virus infection. E1 and E2 undergo modifications such as the addition and removal of oligosaccharides and fatty acids during posttranslational processing.[2]

Because AmB can activate immune modulation by elevating immune response cytokines and pro-inflammatory responses, it may have a role as a potential antiviral drug by acting as antiviral therapy and enhancing immune responses.

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Conflicts of interest

There are no conflicts of interest.

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