BROAD-SPECTRUM THERAPEUTICS FOR VIRAL DISEASES: A MEDICAL COUNTERMEASURE PLATFORM FOR EMERGING THREATS

The Centrality Of Epithelial And Endothelial Barrier Leak In Pathogen-based Disease: Leak Reduction By Elevated Levels Of Tissue-specific Micronutrients As A Prophylactic And Therapeutic Countermeasure

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We recently described how a wide variety of disease pathogens target various epithelial and endothelial tissue barriers to invade the host, spread internally and produce morbidity and mortality directly from barrier compromise (DiGuilio et al., 2022; PMID: 35328419). Lung water accumulation, which figured prominently in COVID and required so many critical care beds, is but one example. Much of this designed targeting of barrier tissues by the pathogen focuses on the tight junction (TJ); a gasket-like, selectively permeable seal that prevents transepithelial/transendothelial leak along the paracellular pathway of mucosal tissues and blood vessels. Pathogens almost universally cause tight junctional leak as a critical part of their etiology. However, a diverse and tissue-specific group of micronutrients can decrease TJ barrier leak in normal mucosal tissues/vessels by junctional remodeling (a phenomenon with important prophylactic implications given that these tissue barriers are the first line of defense that a pathogen must cross to invade a host). Micronutrients can also significantly reduce the barrier leak that ensues from disease progression, whether directly from the pathogen or indirectly from the immune response of the host (a phenomenon with important therapeutic relevance), such as proinflammatory cytokines. This group of barrier-enhancing micronutrients ranges from trace metals such as zinc, to vitamins such as calcitriol and retinoic acid, to diverse flavonoids such as quercetin and resveratrol, to obscure nutraceuticals such as berberine, to name only a few. They are safe, inexpensive, broad-based in their applicability and vetted by a rapidly expanding published literature. They are available for immediate usage and require minimal if any safety testing. Zinc, a micronutrient with well demonstrated ability to decrease gastrointestinal barrier leak, is perhaps the best-developed example. Zinc at normal dietary intake (and RDA level) of 5-10 mg/adult/day is a nutrient supporting normal cellular processes. However, zinc at 50 mg/adult/day (well below the zinc toxicity threshold of 150 mg/adult/day) is essentially a drug, activating specific intracellular signaling pathways that are normally quiescent and generating functional changes that can benefit the host in disease situations. The beneficial changes that are induced, such as TJ remodeling in the gastrointestinal tract, may make initial infection more difficult as well as reduce the TJ leakiness caused by the pathogens directly - or indirectly by the elevated cytokine levels that the pathogen induces. Both altered intracellular signaling pathways and remodeled claudin composition of tight junctions induced by elevated zinc have been well documented. A current need and an opportunity exist for mapping which micronutrients are most effective against which specific pathogens and in which specific tissue beds. This use of elevated micronutrients to reduce barrier leak will neither cure nor fully prevent disease, but it will reduce morbidity. Notably, even a 20% reduction of morbidity may maintain tissue and organ physiology to allow time for one's own immune defenses to neutralize a pathogen. These substances can therefore be highly useful adjuvant therapies, significantly reducing morbidity while also reducing the burden on critical care treatment capacity, particularly at early stages of disease management where targeted anti-viral/anti-bacterial therapeutics are being developed.

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