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ANTI-INFLAMMASOME MICROBES: MINING METAGENOMES FOR THERAPEUTIC CANDIDATES

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The innate immune system's inflammasome is critical since it causes problems when it does not function normally leading to a wide variety of diseases characterized by autoimmunity or chronic inflammation such as metabolic disorders or neurodegenerative diseases. Some pathogenic organisms use strategies to block or reduce the activation of the inflammasome and could serve as potential sources of novel therapeutics. Chronic inflammation is associated with three of the five leading causes of death globally. Additionally, it has been estimated that 5-7% of the population in developed countries has a disease believed to be associated with dysregulation of the immune system. These considerations highlight that there is an acute need to develop new types of therapy for these patients.

The metagenomic analysis of human gut, soil, and marine microbiomes has identified bacterial and viral genes that inhibit inflammasomes. Functional screens using these genes have identified pathogenic effector proteins derived from Yersinia and E. coli that inhibit the assembly of NLRP3 or NLRC4. The global therapeutics market for microbiomes is expected to increase from USD 0.53 billion in 2025 to USD 11.14 billion by 2035 (CAGR 35.7%). The viral proteins F1L and M13L from vaccinia and myxoma viruses contain genes that neutralize NLRP1 and NLRP3, respectively. A high-throughput screen of 2,500 chemical compounds in the European Chemical Biology Library recently identified ten new inhibitors of NLRP3 via caspase-1 and IL-1β assay validation.

Preclinical drug candidates that may be active against the NOD-like receptor (NLRP3) selectively have varying abilities and an example of such is compound 8a, a songorine derivative with an IC_{50} of approximately 2.69 μM in THP-1 and 1.75 μM in J774A.1 cells. Another example is the active component found in the plant Artemisia annua, arteannuin B, which has also been confirmed to selectively target the NLRP3 receptor and produce a beneficial outcome in vivo in both murine models of colitis and lung injury. From the results of virtual screening studies, lead compounds were identified with docking scores as high as -10.438 kcal/mol and significantly greater than control scores (approximately -5.09 kcal/mol). Presently, however, there is no known FDA-approved agent to inhibit NLRP3 and one of the most recent examples is ISM8969, an oral NLRP3 inhibitor for Parkinson's disease which was granted IND status on 1/2026.

There are still some challenges with immunogenicity, off-target effects and delivery; however, using metagenome derived anti-inflammasome candidates presents an exciting new area of exploration. Given that the microbiome therapeutics market is expected to surpass USD 11 billion by 2035, these biological molecules can serve as a new category of targeted treatments for chronic inflammatory diseases. Ongoing interdisciplinary research will be critical to supporting clinical development by way of translation into clinical practice.