Using a common anticonvulsant to counteract inflammation

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Serious conditions, including sepsis, stem from inflammation in the body, and there is a lack of effective medication for sepsis. A chromosomal protein called high-mobility group box 1 (HMGB1),

secreted by immune and dying cells, binds to a specific cellular receptor—receptor for advanced glycation end-products (RAGE)—and triggers the process of inflammation in the body. Through a computer software-based docking study with a structural similarity-based strategy, scientists from Japan, led by senior researcher Prof Sei-ichi Tanuma from Tokyo University of Science (TUS), discovered that the popular anticonvulsant drug papaverine blocks the binding of HMGB1 to this receptor. This kind of "drug repositioning" can be used to find other merits for existing drugs whose safety profiles are known. This novel approach used for the first time here is unique to TUS and is described in the paper published in *Biochemical and Biophysical Research Communications*. Prof Tanuma states, "Our research group has been trying to identify compounds, preferably based on existing drugs, that block the binding of irritants to cellular receptors. We want to find novel drugs to treat inflammation-based conditions."

Inflammation is the body's response to injury or irritation. Although it is technically an "immune response," acute and chronic inflammation are associated with serious conditions and diseases like sepsis, rheumatoid arthritis, diabetes, Alzheimer's disease, and even cancer. One of the many molecular-level processes underlying inflammation is the binding of a RAGE, to a "ligand" (e.g., HMGB1, amyloid β) or irritant. The chromosomal protein HMGB1, which is secreted by immune and dying cells, specifically binds to RAGE and triggers the production of molecules that promote inflammation. These molecules are called pro-inflammatory cytokines (PICs), and this entire cellular mechanism has been implicated in the onset of the diseases and conditions mentioned above.

Sepsis, which is a manifestation of acute infection and inflammation, is a particularly serious concern. Septic shock results in fatal multi-organ dysfunction, and there is still a need for effective drugs to treat septic shock.

This means that molecules that can block the interaction between HMGB1 and RAGE could be a novel class of therapeutics for treating such conditions, especially sepsis. However, it easily takes more than 10 years to get new drugs screened, evaluated, and approved. The concept of "drug repositioning" can be used to overcome this problem. Drug repositioning basically means finding new merits for existing drugs that have known safety profiles. This approach was the basis of this high-profile study done by Prof Tanuma and his colleagues.

The scientists first designed a unique cyclic "peptide" (small protein) called Pepb2 to mimic the RAGE-binding domain of HMGB1, using their computer software called "COSMOS." They found that Pepb2 competed with HMGB1 to bind to RAGE, and thus "competitively inhibited" the HMGB1-RAGE interaction. Then, they screened for Pepb2 mimetic compounds (compounds that are structurally similar to Pepb2) in the DrugBank library. They found that papaverine, a popular vasodilating and anticonvulsant drug extracted from poppy seeds, was structurally similar to Pepb2.

In the laboratory, the researchers then found that papaverine directly blocks the binding of HMGB1 to RAGE and consequently lowers the production of PICs such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α). This proves that papaverine prevents irritants from binding to their receptors and thus suppresses inflammation. Prof Tanuma and colleagues also found that papaverine considerably reduced death rates in model mice with induced sepsis. Prof Tanuma summarizes this research by saying, "This in silico drug design approach, to find novel effects of papaverine, is a unique strategy employed for the first time only by TUS researchers."

In another related study that was also headed by Prof Tanuma, the scientists found that papaverine canceled out the tumor-promoting effects of HMGB1 in tumor microenvironment. They also found that

papaverine suppressed the growth and migration of cancer cells. This study, published in *PLOS ONE*, showed that papaverine may also be a potential anticancer drug.

These findings about papaverine could be a breakthrough in the treatment of diseases like Alzheimer's, diabetes, and cancer, and even sepsis, which is a critical issue in geriatric medicine and emergency medicine. Prof Tanuma concludes, "Drug repositioning using the in silico drug discovery approach used in our research can repurpose existing drugs into novel therapeutic agents. Also, because the cost of 'designing' a novel drug is saved, such approaches can also radically reduce the cost of medical treatment. The next step is to understand the degree to which papaverine blocks HMGB1-RAGE interaction in the human body. We are now trying to optimize the structure of papaverine to design a more 'effective' drug for the future."

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