

## Controlling Excess Inflammation

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*Sepsis is an extremely dangerous clinical condition which occurs when the immune response to an infection becomes so strong that it damages the organs, and this can lead to death when it produces septic shock. A recent discovery could, however, allow us to minimize this damage and could save innumerable lives.*

When encountering **infection** by a microorganism, the immune response unleashes an inflammatory response which permits the neutralization of the pathogen and its elimination from the organism. This phenomenon is absolutely essential to survival, but it must also be strictly controlled because inflammation is extremely irritating to the organs and can cause enormous problems if it becomes excessive.

Sepsis is the best example of damage associated with excessive inflammation. This condition is characterized by an inflammation of very strong intensity, generally triggered by a bacterial, viral or fungal infection, which can quickly lead to the failure of several organs. In North America, about 800,000 people develop sepsis each year and nearly a third of them die of this disease.

### IMMUNE STORM

The Spanish flu pandemic of 1918 is another illustration of the dangers associated with an inflammatory response that is too strong. One of the great mysteries of this pandemic was to understand why the virus preferentially killed the young (20 to 40 years of age), while normally the influenza virus is primarily fatal for infants and the elderly.

It seems that, in individuals who were young and in good health, the virus triggered an "immune storm", characterized by the production of large quantities of biochemical messengers (cytokines) responsible for controlling inflammation. Rather than protect the body from infection, this excessive response led to serious damage to the pulmonary tissue of infected patients, which often led to their deaths.

Similarly, it is interesting to note that the majority of deaths caused by the avian flu virus (H5N1) have so far occurred within persons aged less than 40 years, suggesting that a similar mechanism is responsible.

### MODERATING INFLAMMATION

Currently, the treatment of sepsis essentially consists of stabilizing the general state of the patient, in particular by intravenous



administration of liquids for re-establishing a normal blood volume, combined with therapies to neutralize the pathogenic agent (antibiotics when it is a bacterial infection).

As mentioned earlier, the level of sepsis mortality remains quite high, particularly for severe sepsis or septic shock (failure of several organs) and it is certain that new therapeutic approaches are necessary to improve the survival of people who develop these conditions.

### A RAY OF HOPE

A study recently published in the prestigious journal *Science* offers a ray of hope for this<sup>1</sup>. Because it is the excess inflammation which puts the lives of patients in danger, a team of American scientists had the bright idea of targeting the inflammation itself rather than the pathogenic agent responsible for the inflammation, as is usually the case.

This strategy seemed to work: they observed that a compound which blocks the function of an enzyme essential for the activation of inflammation (Topoisomerase-1) is capable of suppressing the immune response in the host against both bacteria and viruses. This action seems to be quite promising for the treatment of sepsis, because injection of the compound into animals suffering from sepsis was able to save the lives of nearly 90% of them, without any noticeable secondary effects.

These results suggest that therapies based on the inhibition of topoisomerase-1 could eventually save many of the people afflicted with sepsis, as well as considerably reduce the deaths caused by certain virus pandemics such as the 1918 influenza pandemic, capable of unleashing such destructive "immune storms".

<sup>(1)</sup> Rialdi, A et al. Topoisomerase 1 inhibition suppresses inflammatory genes and protects from death by inflammation. *Science* 2016;352:7993.