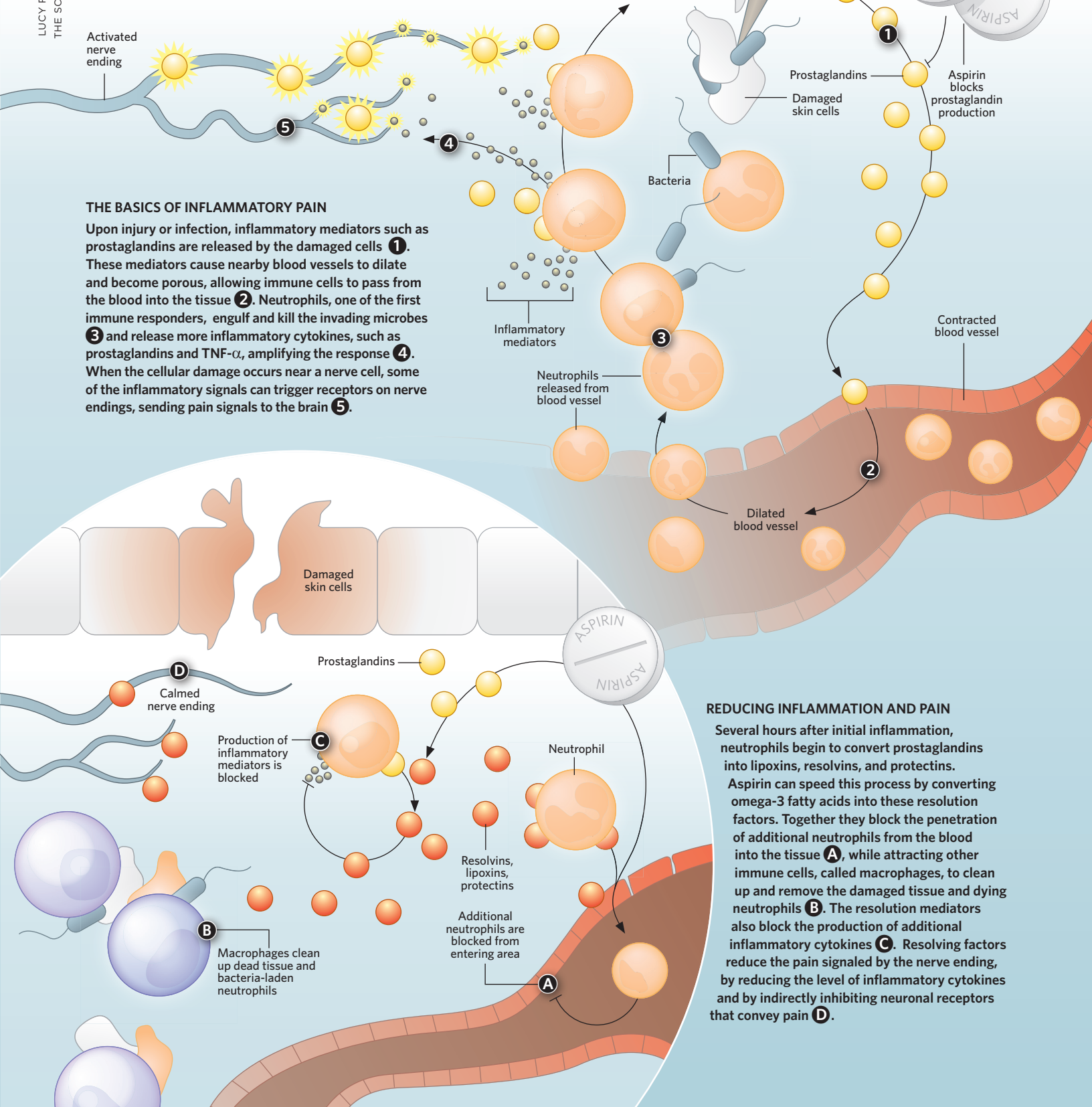


INFLAMMATION, PAIN, AND RESOLVINS

Not all inflammation leads to pain. Despite widespread infection followed by fever, colds rarely cause pain. But when some cytokines and certain immune cells are active near pain-sensing nerves, they trigger receptors that convey pain sensations to the brain. Resolvins are naturally produced part-way into an inflammatory reaction, and help diminish inflammation as well as pain.



THE BASICS OF INFLAMMATORY PAIN

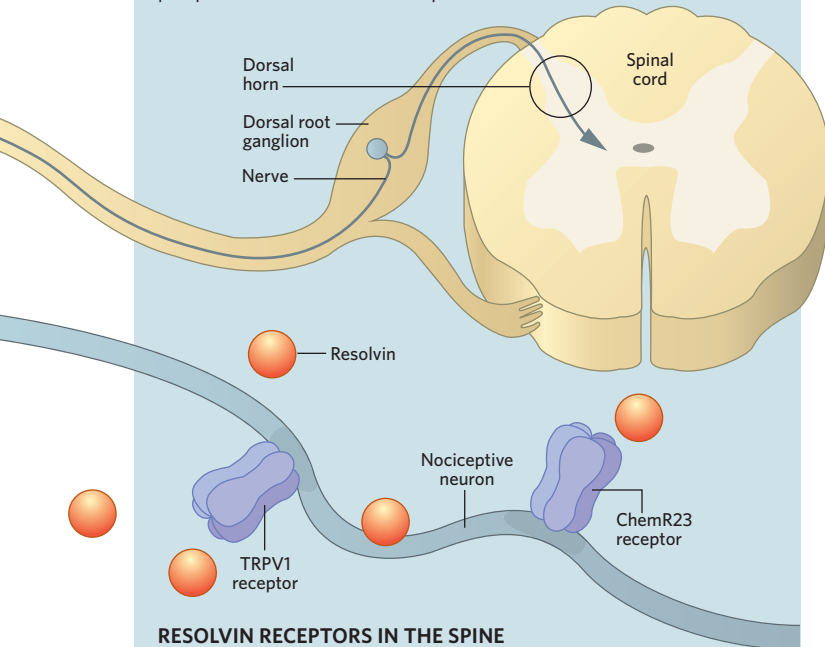
Upon injury or infection, inflammatory mediators such as prostaglandins are released by the damaged cells **1**. These mediators cause nearby blood vessels to dilate and become porous, allowing immune cells to pass from the blood into the tissue **2**. Neutrophils, one of the first immune responders, engulf and kill the invading microbes **3** and release more inflammatory cytokines, such as prostaglandins and $\text{TNF-}\alpha$, amplifying the response **4**. When the cellular damage occurs near a nerve cell, some of the inflammatory signals can trigger receptors on nerve endings, sending pain signals to the brain **5**.

REDUCING INFLAMMATION AND PAIN

Several hours after initial inflammation, neutrophils begin to convert prostaglandins into lipoxins, resolvins, and protectins. Aspirin can speed this process by converting omega-3 fatty acids into these resolution factors. Together they block the penetration of additional neutrophils from the blood into the tissue **A**, while attracting other immune cells, called macrophages, to clean up and remove the damaged tissue and dying neutrophils **B**. The resolution mediators also block the production of additional inflammatory cytokines **C**. Resolving factors reduce the pain signaled by the nerve ending, by reducing the level of inflammatory cytokines and by indirectly inhibiting neuronal receptors that convey pain **D**.

RESOLVINS IN CHRONIC PAIN

Chronic pain is a complicated disorder that can be influenced as much by mood and personal experience as it can by persistent inflammation or unresolved pain. In some cases when pain is constantly relayed through the peripheral nerves to the central nervous system, a sort of imprint or pain memory is created, leading to chronic pain. Resolvins can dampen the nerve transmission that leads to chronic pain by acting both at the peripheral nerve and in the spine.



RESOLVIN RECEPTORS IN THE SPINE

Resolvins have been shown to act by indirectly inhibiting the capsaicin receptors called transient receptor potential vanilloid 1 (TRPV1). But they may also reduce inflammation by acting on the ChemR23 receptor, which is expressed along with the TRPV1 receptor on the dorsal horn of the spinal cord. Although it is unclear exactly how the ChemR23 receptor interacts with the TRPV pathway, it appears to be important for the pain-relieving activity of resolvins by blocking the signaling protein ERK.