Uncovering the dark side of TNF

In the early 1980s, in search of the cytokine that triggers disease-associated weight loss and lethal shock, Anthony Cerami and Bruce Beutler purified “cachectin.” They soon found out that their malevolent cytokine already had another name—tumor necrosis factor (TNF)—and was being lauded as a potential antitumor agent.

The bright side
Although TNF itself was not discovered until the 1970s, a physician named William Coley first noted the phenomenon of tumor necrosis at the turn of the 20th century. The tumors of some of his cancer patients shrank after they had acquired streptococcal infections (1). But the inherent dangers of injecting humans with a toxic soup of bacterial endotoxins prevented Coley’s observation from being converted into an antitumor therapy. Researchers, however, hoped to separate the tumor-blasting factor from the toxic mess. Lloyd Old and his team at the Memorial Sloan Kettering Cancer Center (New York, NY) finally zeroed in on serum TNF from bacterium-primed, endotoxin-challenged mice in 1975 (2).

TNF was immediately included with the likes of interferon-γ, IL-2, and monoclonal antibodies as the next best hope in cancer treatment. By the mid-1980s, it was being tested on cancer patients all over the world. The results, however, were lackluster. TNF therapy not only failed to shrink tumors but also caused side effects. And just across the street from Sloan Kettering, a group from Rockefeller University headed by Anthony Cerami would soon publish data that would put a further damper on the TNF-as-cure idea.

The “wasting” connection
Cerami had not started out trying to expose TNF’s seamer side. His main interest was in understanding the basis of cachexia—the weight loss associated with many chronic diseases, such as cancer and tuberculosis. In the 1970s, while testing drugs designed to rid cattle of the parasite Trypanosoma, Cerami noticed that the animals continued to waste away even though the parasites were dying off. The continued weight loss was not drug induced, as parasite-infested antelopes also responded to the drug but showed no further wasting. Cachexia, Cerami surmised, might be due to a host factor that was meant to fight the infection but became a threat when produced in amounts that overwhemed the body.

Cerami soon found a reliable biochemical read-out for cachexia: lipaemia, the accumulation of lipids in the blood due to the suppression of a fat-metabolizing enzyme (3). The hypothetical host factor, Cerami realized, might be suppressing this enzyme, lipoprotein lipase (LPL), thus triggering a fat storage problem and cachexia. He and a post-doctoral associate, Masanobu Kawakami, tested this hypothesis in a mouse model of endotoxin-induced cachexia. Mice that were genetically susceptible to endotoxin had deficient LPL activity after an injection of bacterial lipopolysaccharide (LPS), whereas endotoxin-resistant mice had normal LPL activity. Serum from LPS-treated sensitive mice triggered LPL suppression in normally resistant mice, suggesting the presence of the cachexia-inducing host factor in the serum.

A cytokine by any other name
The task of purifying this mystery protein was taken up by Bruce Beutler, another of Cerami’s post-doctoral associate. The team had previously found that a macrophage cell line produced copious amounts of the LPL-suppressing factor when stimulated by endotoxin (4). The macrophage prep was also a better starting point for protein purification compared with the messy mouse serum. Beutler then took a year to purify the protein, which the team named “cachectin.” They published their discoveries in the Journal of Experimental Medicine (5, 6).

Beutler sequenced cachectin and initially thought he was dealing with a unique protein. The team’s collaborators at the Scripps Institute (La Jolla, CA), however, found that cachectin shared the same biological activity with TNF. A comparison of cachectin’s sequence with that of the newly sequenced human TNF solidified the link. The team added this later discovery as a footnote to their already-accepted paper (5).

Therapy becomes therapeutic target
The identification of cachectin as the benign cytokine TNF created a furor in the field, especially as the other biological activities of cachectin mimicked the side effects seen in the TNF-treated cancer patients. “Everyone else was advocating for TNF to be given to patients,” says Cerami. “We wanted to get rid of it.” His team later found that blocking TNF activity using antibodies reduced infection-induced inflammation and endotoxin-induced lethality (7). Today, anti-TNF drugs are successfully used in the treatment of inflammatory diseases such as rheumatoid arthritis and psoriasis.

REFERENCES