IN-DEPTH LOOK: ANTI-TNF-α THERAPIES

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1. INTRODUCTION

1.1 Tumor Necrosis Factor-α Discovery

Long before the discovery of *tumor necrosis factor-α* (TNF-α), a German physician named P. Bruns reported the regression of tumors after bacterial infection. This led an American oncologist, William Coley, to use bacterial extracts (referred to as Coley's toxins) for the treatment of human cancers [1]. William Coley first observed the phenomenon of tumor necrosis when he saw that the tumors of some of his cancer patients shrank after they had acquired streptococcal infections. Subsequently, in 1975, Lloyd Old and his colleagues, at Memorial Sloan Kettering Cancer Center, identified the TNF-α in the serum of bacterium-primed, endotoxin-challenged mice [2]. It was classified along with other cytokines, such as interferon-γ (IFN-γ) and interleukin-2 (IL-2). Due to its ability to cause tumor necrosis TNF-α soon became the next best hope in cancer treatment. It was tested on cancer patients all over the world, but the results were not as promising as expected.

At the same time, another group at Rockefeller University, headed by Anthony Cerami, was trying to unravel the basis of cachexia—a wasting syndrome associated with many chronic diseases such as cancer, human immunodeficiency virus–acquired immunodeficiency syndrome (HIV–AIDS), tuberculosis (TB), and the like. He found that cachexia was associated with lipemia, the accumulation of lipids in the blood due to suppression of the fat-metabolizing enzyme lipoprotein lipase (LPL) [3], and conjectured that the same factor, which is causing cachexia, is also suppressing LPL, thus triggering lipemia. Furthermore, he had surmised that cachexia and associated lipemia might be due to a protective factor produced by the host in order to fight the infection, but its chronic production became a threat to the body. They tested and validated this hypothesis in a mouse model of endotoxin-induced cachexia [4]. Later, one of Cerami's postdoctoral associates, Bruce Beutler, successfully isolated this factor and their team named this factor as "cachetin" [5, 6]. It was thought to be a unique protein until Beutler sequenced it and found that its sequence was similar to that of human TNF-α discovered earlier by Old's group [7]. The biological activities of TNF-α and cachetin were also found to be alike [8].

The rediscovery of TNF-α as cachetin and elucidation of its role in cachexia explained the side effects seen in cancer patients treated with TNF-α [9]. Beutler's team later found that blocking TNF-α activity using antibodies reduced infection-induced inflammation and endotoxin-induced lethality [10]. Cloning of TNF-α by Goeddel and colleagues in 1984 made sufficient recombinant materials available for study [11]. The studies demonstrated that TNF-α was a multifunctional cytokine that mediates key roles in acute and chronic inflammation and infection. Today, anti-TNF-α drugs are being successfully used in the treatment of various inflammatory diseases such as rheumatoid arthritis (RA) and Crohn's disease. In later years, research showed that TNF-α is involved in the progression of cancer in many

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