

9 TNF- α in CNS: Physiologic and Pathologic Roles

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Abstract: Tumor necrosis factor-alpha (TNF- α) is a pleuripotent cytokine credited with diverse functions ranging from neuromodulatory roles in a normal brain to immune-responsive Janus-faced involvement in a diseased brain where studies have exposed its neuroprotective as well as its neurodegenerative influences. This chapter aims at illuminating these functions and establishing TNF- α and its receptors (TNF system) as a major proctor of central nervous system (CNS) function.

List of Abbreviations: ACTH, adrenocorticotrophic hormone; AD, Alzheimer's disease; AP-1, activator protein-1; BBB, blood-brain barrier; c-IAP, cellular inhibitor of apoptosis protein; CNS, central nervous system; COX-2, cyclooxygenase-2; DED, death effector domain; DISC, death-inducing signal complex; FADD, Fas-associated death domain; HAD, HIV-associated dementia; IKK, I κ B kinase; iNOS, inducible nitric oxide synthase; JNK, c-Jun N terminal kinase; LPSs, lipopolysaccharides; LTD, long-term depression; LTP, long-term potentiation; MS, multiple sclerosis; mTNF- α , membrane-bound TNF- α ; NEMO, NF- κ B essential modifier; NF- κ B, nuclear factor-kappaB; NGF, nerve growth factor; NIK, NF- κ B-inducing kinase; NREM, nonrapid eye movement; PD, Parkinson's disease; PI3K, phosphatidylinositol-3-kinase; RIP1, receptor-interacting protein 1; SDF-1, stromal-derived factor-1; SODD, silencer of death domain; sTNF- α , soluble TNF- α ; TNF- α , tumor necrosis factor-alpha; TNF-R, TNF- α receptor; TACE, TNF- α converting enzyme; TRADD, TNF-R-associated death domain; TRAF2, TNF-R-associated factor 2

1 Historical Perspective

To the credit of physician William Bradley Coley, the antitumor property of the immune response was identified and clinically utilized more than 100 years ago (Coley, 1891). Coley, the third surgeon-in-chief in New York hospital for special surgeries, reported back in 1893 that cancer patients who developed bacterial infections showed necrosis of tumors. He himself attempted to treat such patients with filtrates of cultured Gram-negative bacteria, which he later marketed under the brand name "Coley Mixed Toxin." Even after Coley's death in 1936, the product was available in USA until the 1960s as a cancer vaccine. However, the vaccine lost its way in history mainly due to extensive side effects generated by its administration. Subsequent to the Coley episode, it took more than three quarters of a century after the surgeon's pioneering report to identify the active principle behind the tumor killing aspect of immune response. In 1975, the active element was identified as a serum constituent of bacillus Calmette-Guérin-treated mice that mimicked lipopolysaccharide (LPS)-induced dramatic hemorrhagic necrosis of solid tumors overnight (Carswell et al., 1975). Owing to this property, the century-old antitumor immune component finally derived the name tumor necrosis factor (TNF). Identified later as a glycoprotein released from host macrophages (Oettgen et al., 1980), TNF- α was found to be the same molecular moiety that was otherwise identified as hormone cachectin secreted from macrophages (Beutler et al., 1985a, b) and had structural and functional relationships with human lymphotoxin- α (later renamed as TNF- β) (Pennica et al., 1984). Subsequently, the cloning of complementary DNA (cDNA) and amino acid sequencing of this cytokine was simultaneously undertaken by several laboratories in the 1980s (Pennica et al., 1985; Haranaka et al., 1986; Aggarwal et al., 1987). The following years saw a rush of information about this protein and by the end of a decade, the therapeutic potential of this acclaimed wonder drug for cancer was also being estimated in other fields as it became clear that, contrary to its name, TNF- α did not induce necrosis or apoptosis in most cell types, including many tumor cells. This paved the pathway for anticytokine therapy, where antibodies generated against TNF- α were shown to prevent bacterial sepsis (Beutler et al., 1985a, b; Tracey et al., 1987), rheumatoid arthritis (RA) (Elliott et al., 1993), and other inflammatory diseases like Crohn's disease (van Dullemen et al., 1995). Involvement of TNF- α in brain function was proposed in the late 1980s and since then a plethora of information has accumulated about the biology and functions of this molecule in the brain. Before discussing its role in the central nervous system (CNS), a brief summary of properties of this cytokine, its receptors, and its signal transduction pathways is presented in the following sections.

AU1

AU2

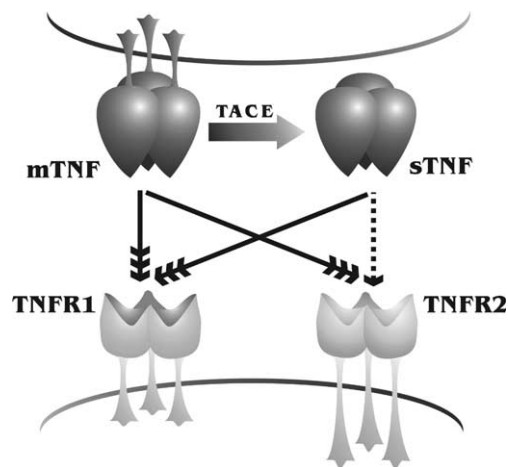
2 Biology of TNF- α

2.1 The Molecule

TNF- α is the prototypical cytokine member of a family of structurally related biomolecules (TNF ligand superfamily) with conserved bioactivity among vertebrates (Goetz et al., 2004). Human TNF- α is translated as a 233-amino-acid, 26-kDa proprotein that is displayed on the plasma membrane as a type II transmembrane moiety (Kriegler et al., 1988). Membrane-bound form of TNF- α (mTNF- α) is then cleaved by a nonspecific metalloproteinase called TNF- α converting enzyme (TACE) in the extracellular domain to release the 157-amino-acid, 17.3-kDa soluble (sTNF- α) monomer (Figure 9-1) (Moss et al.,

Figure 9-1

TNF receptor–ligand interplay. TNF- α is displayed on the membrane as biologically active homotrimers (membrane-bound TNF- α , mTNF) that may be cleaved by metalloproteinase TNF- α converting enzyme (TACE) to release soluble homotrimers (sTNF), which are also active biologically. Two TNF receptors (TNFR1 and TNFR2) have various binding affinity for the ligand. While mTNF has equal affinity for both the receptors, sTNF displays greater affinity for TNFR1



1997). This 17-kDa monomer is composed of two antiparallel β -pleated sheets with antiparallel β -strands forming a “jelly roll” structure typical of few viral capsid proteins and the TNF ligand family. Both the membrane-bound and secreted forms retain biological activity of the molecule. However, such biological activity is contingent on oligomerization of the molecule into conical homotrimers such that each monomer contacts the remaining two. Adding the soluble form, this cleaved product exists in solution as a homotrimer of total molecular mass of 52 kDa. Trimers are assembled intracellularly before their membrane display or TACE-mediated cleavage (Tang et al., 1996). Mutational analyses have identified three receptor interaction domains in monomer–monomer interface near the base of the trimer structure (Idriss and Naismith, 2000). We will discuss more about TNF- α ligand–receptor interaction in the next section.

Normal and tumor cells of both hematopoietic and nonhematopoietic origin express TNF- α . This includes immune cells like T cells, B cells, dendritic cells, natural killer (NK) cells, neutrophils, eosinophils, and mast cells. In brain, neurons and glial cells express TNF- α under normal conditions, while in diseased state TNF- α production is greatly enhanced in activated astroglia and microglia.