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Current Topic

Human Tumour Necrosis Factor: Physiological and Pathological Roles in Placenta and Endometrium

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ABSTRACT

The cytokine tumour necrosis factor α (TNF) is a well known member of the TNF superfamily consisting of at least 18 ligands and 29 different receptors involved in numerous cellular processes. TNF signals through two distinct receptors TNFR1 and TNFR2 thereby controlling expression of cytokines, immune receptors, proteases, growth factors and cell cycle genes which in turn regulate inflammation, survival, apoptosis, cell migration, proliferation and differentiation. Since expression of TNF was discovered in amnion and placenta many studies demonstrated the presence of the cytokine and its receptors in the diverse human reproductive tissues. Whereas TNF has been implicated in ovulation, corpus luteum formation and luteolysis, this review focuses on the functions of TNF in human placental, endometrial and decidual cell types of normal tissues and also discusses its role in endometrial and gestational diseases. Physiological levels of the cytokine could be important for balancing cell fusion and apoptotic shedding of villous trophoblasts and to limit trophoblast invasion into maternal decidua. Regulation of the TNF/TNFR system by steroid hormones also suggests a role in uterine function including menstrual cycle-dependent destruction and regeneration of endometrial tissue. Aberrant levels of TNF, however, are associated with diverse reproductive diseases such as amniotic infections, recurrent spontaneous abortions, preeclampsia, preterm labour or endometriosis. Hence, concentrations, receptor distribution and length of stimulation determine whether TNF has beneficial or adverse effects on female reproduction and pregnancy.

1. Human tumour necrosis factor

Tumour necrosis factor (TNF, cachexin or cachectin and formerly known as tumour necrosis factor-α) is a pleiotropic inflammatory cytokine. It was first isolated by Carswell et al. in 1975 in an attempt to identify cytotoxic factors responsible for necrosis of the sarcoma Meth A [1].

1.1. Structure and general function

The human TNF gene was cloned in 1984 and maps within the major histocompatibility complex to Chromosome 6p21.3 [2]. It spans about 3 kb and consist of 4 exons whereas the last exon codes for more than 80% of the secreted protein [3]. At this time its homology to another factor cytotoxic to tumour cells, TNF-β (also

Abbreviations: ASK-1, apoptosis-signalling kinase-1; AP-1, activator protein-1; bFGF, basic fibroblast growth factor; cIAP, cellular inhibitor of apoptosis protein; COX-2, cyclooxygenase-2; CRH, cortisol releasing hormone; ECM, extracellular matrix; EGF, epidermal growth factor; EMT, epithelial-mesenchymal transition; ERK, extracellular regulated kinases; Etk, endothelial/epithelial kinase; EVT, extravillous trophoblast; GnRH, gonadotropin-releasing hormone; HB-EGF, heparin-binding EGF-like growth factor; hCG, human chorion gonadotrophin; HLA, human leukocyte antigen; ICM, inner cell mass; IGF-1, insulin-like growth factor 1; IkB, inhibitor of kB; INFγ, interferon-γ; IUGR, intra-uterine growth restriction; JNK, c-Jun N-terminal kinase; LPS, lipopolysaccharide; MAP, mitogen activated protein; MCP-1, monocyte-chemotactic protein-1; MEKK, MAP kinase kinase kinase; MHC, major histocompatibility complex; MIF, migration inhibitory factor; MMP, matrix metallo proteinase; NFκB, nuclear factor kappa B; NK cells, natural killer cells; PAI-1, plasminogen activator inhibitor 1; PCOS, polycystic ovary syndrome; PDGF, platelet-derived growth factor; PG, prostaglandin; PI3K, phosphoinositid-3-kinase; RANTES, regulated upon activation normal T-cell expressed and secreted; RIP-1, serine/threonine kinase receptor interacting protein-1; SNP, single nucleotide polymorphism; SODD, silencer of death domain; STB, syncytiotrophoblast; sTNF, soluble tumour necrosis factor alpha; TACE, TNF-converting enzyme; TGF, transforming growth factor; Th1, T helper; Th1, T helper 2; TNF, tumour necrosis factor alpha; TNFR1, tumour necrosis factor receptor 1; TNFR2, tumour necrosis factor receptor 2; TRADD, TNFR-associated death domain; TRAF2, TNF receptor-associated factor 2; TRAIL, TNF-related apoptosis-inducing ligand; TUNEL, TdT-mediated dUTP-biotin nick end labelling; UAP, uterine activation protein; uPA, urokinase-type plasminogen activator; VCAM, vascular cell adhesion molecule; vCTB, villous cytotrophoblast; vEGF, vascular endothelial growth factor; vSMC, vascular smooth muscle cells; XAF1, XIAP associated factor 1; XIAP, X-linked inhibitor of apoptosis.

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termed lymphotoxin) was noticed [2]. Whereas TNF is mainly produced in monocytes and/or macrophages, TNF-β is a product of lymphoid cells, but binds to the same surface receptor as TNF [4]. Both proteins have similar biological activities [3] but investigation of their structures revealed that TNF-β is a glycoprotein that has no cysteine residues whereas TNF contains one disulphide bond [5]. In vitro site mutagenesis of these cysteine residues demonstrated that the disulfide bond is important for the biological function of TNF [6]. Throughout the years, however, it became clear that both proteins belong to a superfamily of soluble TNF ligands comprising at least 18 different members controlling diverse cellular functions such as apoptosis, inflammation, sepsis and development of the immune system [7].

The TNF protein is a homotrimer primarily produced as a 212 amino acid type II transmembrane protein [8,9]. Three monomers associate around a 3-fold axis to form a compact bell-shaped trimer. This structure is typical for members of the TNF family but comparison to known protein structures also showed structural homology to several viral coat proteins [10]. TNF can act in its membrane-bound form through cell-to-cell contact or after cleavage from the cell membrane as a soluble 51 kDa homotrimer (sTNF). Cleavage is carried out by the metalloproteinase TNF alpha converting enzyme (TACE, also called ADAM17) [11]. The homotrimeric sTNF dissociates at concentrations below the nanomolar range, thereby losing its bioactivity. The cytokine is predominantly produced upon activation of myeloid cells, e.g. macrophages, but also by endothelial cells, fibroblasts and neuronal tissue.

TNF exhibits its biological properties upon binding to its cognate membrane receptors TNFR1 (TNFRSF1A, CD120a, p55) and TNFR2 (TNFRSF1B, CD120b, p75) which are members of the TNF receptor superfamily [12]. This superfamily consists of at least 29 transmembrane proteins which are activated through the different TNF superfamily ligands and signal through six different members of a family of intracellular mediators termed TNFR associated factors (TRAFs). A hallmark of the TNFR superfamily is cysteine-rich regions in their extracellular domain including 6 highly conserved cysteine residues [13]. TNFR1 and TNFR2 contain each four cysteine-rich repeats [14]. Like the TNF ligands, the receptors also form a trimeric structure. It was long believed, that the ligand recruits three receptor monomers into the final 3:3 complex [12] being the key event for initiation of signal transduction. However, recent evidence indicated that a distal cysteine-rich domain which is called PLAD (pre-ligand binding assembly domain) keeps TNFR1 and TNFR2 in a pre-assembled oligomeric status avoiding causeless auto-activation [15]. Upon ligand binding the receptor undergoes a conformational change towards a higher-order receptor complex achieving signal competence [16]. TNFR1 is constitutively expressed in most tissues and seems to be the key mediator of TNF signalling. In contrast, TNFR2 is strongly regulated and predominantly found in immune cells indicating that this receptor plays a major role in the lymphoid system [17]. The extracellular domains of both receptors can also be cleaved from the membrane resulting in the production of soluble TNF (sTNF) receptors. The secreted proteins eventually neutralize TNF, even though their binding affinities are much lower than those of the membrane receptors [18]. Whereas TNFR2 is cleaved by TACE [19], the proteolytic enzyme releasing sTNFR1 is still unknown. Shedding of sTNFR1 seems to be physiologically important since mutations leading to cleavage resistance are related to dominantly inherited autoinflammatory syndromes (TNFR1-associated periodic syndromes) [20].

TNF has a wide spectrum of bioactivities and most cells show at least some response sensitivity to TNF (Fig. 1). In general, the cytokine displays a functional duality being involved in tissue regeneration and destruction [16]. Under physiological conditions, TNF is involved in immune surveillance and defence, in cellular homeostasis, protection against certain neurological insults as well as in the control of cell survival, proliferation, migration and differentiation [21]. Owing to its strong pro-inflammatory and immuno-stimulatory activities, TNF is associated with a number of pathological events. The cytokine is involved in the progression of many autoimmune diseases, e.g. rheumatoid arthritis and inflammatory bowel diseases [22,23]. Hence, usage of sTNF receptors and TNF-neutralising antibodies became important therapeutic strategies for these disorders [24].

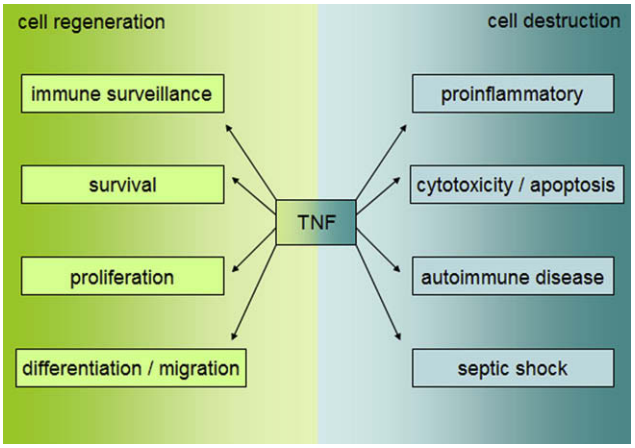

Fig. 1. The diverse biological effects of TNF. Beneficial vs. adverse effects depend on local TNF concentrations, the expression pattern of TNF receptors and the abundance of inhibitors such as sTNFRs.

In general, TNF concentrations seem to determine whether the cytokine exerts beneficial or harmful effects. High doses of sTNF in response to lipopolysaccharides and other bacterial toxins play a key role in the development of septic shock [25]. Low concentrations over a long period of this particular cytokine are often associated with cachexia (i.e. weakness, loss of weight and muscle atrophy) which can be found in tumour patients [26]. All the different well described roles of TNF indicate that there must be a complex interaction pattern between TNF concentration, tissue and cell type, TNF receptor distribution and duration of TNF stimulation leading to a specific physiological or pathological reaction.

1.2. TNF-dependent signalling pathways

TNF signalling is mediated through TNFR1 and TNFR2 (Fig. 2). Although both receptors contain a highly homologous, cysteine-rich extracellular domain, their intracellular regions do not show sequence homology [27]. The two receptors are differentially expressed on cells and overlapping as well as distinct signal transduction was observed. However, general differences between TNFR1- and TNFR2-dependent signalling were noticed. Activation of TNFR1 basically leads to pro-inflammatory as well as programmed cell death pathways, both associated with tissue injury. Signalling through TNFR2 can induce apoptosis but also support survival promoting tissue repair and angiogenesis [28].

1.2.1. TNFR1-dependent signalling

The cytoplasmic domain of the unstimulated receptor is bound by silencer of death domain (SODD) preventing constitutive signalling of TNFR1 [29]. Upon TNF stimulation, SODD is released and TNFR-associated death domain protein (TRADD) binds to the intracellular domain followed by recruitment of the serine/threonine kinase receptor interacting protein-1 (RIP-1) [30], TRAF-2, as well as of cellular inhibitor of apoptosis proteins cIAP1 and cIAP2. This protein complex, termed complex I, is considered to activate the NFκB pathway via MAP (mitogen activated protein) kinase