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How T-lymphocytes are activated and become activators by cell-cell interaction

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Immunological descriptions support the role of direct contact between T-lymphocytes and monocytes at the site of inflammatory lesions. The following will therefore focus on the role of direct contact between stimulated T-lymphocytes and monocytes in the production of cytokines and cytokine inhibitors, as well as matrix metalloproteinases (MMPs) and tissue inhibitor of metalloproteinases (TIMP) by monocytes. The role of T-lymphocytes and polymorphonuclear neutrophils (PMN), endothelial cells and fibroblast-like cells will also be discussed. Blocking the interaction between T-lymphocytes and monocytes may provide a useful approach to therapeutic intervention.

Introduction

In many chronic inflammatory diseases, inflammation is characterised by the influx into the target tissue of immune cells such as dendritic cells, T- and B-lymphocytes, granulocytes, and mononuclear phagocytes. This influx of inflammatory cells in the target tissue is associated with the proliferation of invading and resident cells, and frequently with destruction and remodelling of the extracellular matrix. Tissue destruction is ruled by proteases, mainly MMPs. The expression of these proteases and their inhibitors (TIMPs) is controlled by many factors including cytokines, contact with extracellular matrix components and direct cell-cell contact [1, 2]. In pathological conditions, the production of cytokines and MMPs by infiltrating and resident tissue cells escapes regulatory mechanisms. The activity of proinflammatory cytokines is counterbalanced by numerous mechanisms including cytokine inhibitors. It is generally acknowledged that imbalance between cytokines and their respective inhibitors is responsible for the persistence of chronic inflammatory conditions if not required for its initiation. There is now considerable evidence that cytokines, such as tumour necrosis factor (TNF)-α and interleukin (IL)-1β and -1α are involved in tissue destruction in many chronic inflammatory diseases affecting various organs.

Cytokines such as TNF-α and IL-1β play an essential role in inflammation and are mainly produced upon activation of monocyte-macrophages. In immunoinflammatory diseases, in the absence of infectious agents, the factors triggering TNF-α and IL-1 production are still elusive. However, T-cell cytokines such as IL-4, -10, and -13 have predominantly anti-inflammatory effects, and alone, interferon (IFN)-γ, IL-2, -15, or -17 display weak activation capacity in terms of IL-1β and TNF-α induction. This has prompted the author′s group to hypothesise and to demonstrate that T-cells exert a pathological effect through direct cellular contact with monocyte-macrophages, inducing massive upregulation of IL-1 and TNF-α [3–6], such that the production of TNF-α and IL-1β induced in monocytes by membranes isolated from blood-derived stimulated T-lymphocytes or stimulated T-cells (HUT-78) was equivalent to that induced by lipopolysaccharides [1]. Besides triggering proinflammatory cytokine production, contact-mediated activation of monocytes induced the production and/or shedding of cytokine inhibitors such as IL-1-receptor antagonist (IL-1Ra), and soluble receptors of IL-1 and TNF-α [7–9].

T-lymphocyte signalling of monocyte-macrophages by direct cell-cell contact

The relevance of T-lymphocytes/monocyte interaction is illustrated by different chronic inflammatory diseases, affecting osteoarticular structures, lung parenchyma and the central nervous system, where T-lymphocytes are likely to play a pivotal role [10–12]. In the mid-1980s, it was observed that the expression of membrane-associated IL-1 (IL-1α) in mouse monocytes was mediated by both soluble factors and direct contact with T-cells [13]. The importance of cellular contact was confirmed by experiments showing that IL-1 was induced upon T-cell-monocytes contact with both T-helper cell (Th) type-1 and -2 cells in the absence of lymphokine release [14]. In human cells, direct contact with leptin-stimulated T-cells proved a potent stimulus of monocyte activation [3, 4]; the production of IL-1β by human monocytes also depending on the direct contact with anti-CD3-stimulated T-cells [15]. Following observations made by the author′s group and others, several studies were carried out in human cells that have confirmed the importance of T-cell contact-mediated cytokine induction in monocytes. Studies have led to the concept that based on their effect on monocytes, T-lymphocytes can be classified as cytokine-activated T-lymphocytes or T-cell receptor-activated T-lymphocytes [16].

Most T-cell types including T-cell clones, freshly isolated T-lymphocytes and T-cell lines, such as HUT-78 cells, induce IL-1 and TNF-α in monocytes [3–6]. Various stimuli other than phytohaemagglutinin (PHA)/phorbol myristate acetate (PMA) induce T-lymphocytes to activate monocytes by direct cellular contact including: 1) cross-linking of CD3 by immobilised anti-CD3 monoclonal antibody with or without cross-linking of the co-stimulatory molecule CD28 [9, 16–18]; 2) antigen recognition on antigen-specific T-cell clones [9]; and 3) cytokines [19–21]. Furthermore, depending on T-cell type and T-cell stimulus, direct cell-cell contact with stimulated T-lymphocytes can induce different patterns of products in monocytes. This suggests that multiple ligands and counter-ligands are involved in the contact-mediated

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activation of monocytes, which are differentially induced in T-cells depending on the stimulus. Imbalance in the production of proinflammatory *versus* anti-inflammatory cytokines has also been observed, where Th1 cell clones preferentially induced IL-1β rather than IL-1Ra production [9], and cytokine-stimulated T-lymphocytes induced TNF-α production while failing to produce IL-10 [19]. It was also demonstrated that upon contact with stimulated T-cells the balance between IL-1β and IL-1Ra production in monocytes is ruled by Ser/Thr phosphatase(s) [7] and that contact-activated human acute monocytic leukaemia cell line (THP)-1 cells express membrane-associated protease(s) neutralising TNF-α activity both by degrading the latter cytokine and by cleaving its receptors at the cell surface [8]. Thus, the triggering of these intra- and extracellular processes by direct contact with stimulated T-lymphocytes may regulate the proinflammatory cytokines and their inhibitors, and the balance of their production in monocytes dictates in part the outcome of the inflammatory process.

Cell surface molecules involved in contact-mediated monocyte activation

A crucial issue arising from these observations is the identity of the molecules on the T-cell surface that are involved in contact-mediated signalling of monocyte activation as well as their counter-ligands. It has been postulated that T-cell membrane-associated TNF-α was involved in monocyte activation. However, fixed, stimulated Th2 cells from a T-cell line that did not express membrane-associated TNF induced both TNF and IL-1 production in monocytes [22] demonstrating that TNF-α may play a part but not a primary one. The author′s group has shown that neither soluble TNF-α receptors nor IL-1Ra block T-cell signalling of the monocytic cell line THP-1. Moreover, neutralising antibodies to TNF-α, IL-1, IL-2, IFN-γ and granulocyte/macrophage colony-stimulating factor all failed to affect monocyte activation by membranes from stimulated T-cells [3, 4, 11].

In addition to membrane-associated cytokines, other surface molecules have been assessed as to their ability to activate monocytes upon contact with stimulated T-cells, *e.g.* leukocyte function antigen (LFA)-1/intercellular adhesion molecule (ICAM)-1, CD2/LFA3, CD40/CD40L and lymphocyte activation-antigen-3 (LAG-3). Thus, CD40/CD40L interaction was shown to be involved in the contact activation of both human and mouse monocytes by T-lymphocytes stimulated for 6 h [23]. However, when stimulated, T-lymphocytes isolated from both CD40L-knockout and wildtype mice triggered monocyte activation, although to a lower extent [24]. In the author′s system, where stimulated human T-lymphocytes proved to have a high capacity of inducing cytokines in monocytes, inhibition of contact-induced cytokine production was never observed, whether by blocking antibodies to CD40L or soluble CD40. Furthermore, HUT-78 cells, which efficiently induce cytokine production in monocytes, do not express CD40L messenger ribonucleic acid in resting or activated conditions [25]. Finally, THP-1 cells that respond to contact-mediated activation by membranes of stimulated T-cells do not express CD40.

Another study showed that in cocultures of living cells stimulated with IL-15, Th1 unlike Th2 clones induce IL-1β production in monocytes [21]. In the latter system, blockade of the CD40-CD40L interaction results in inhibition of IL-1β production while IL-1Ra induction is unaffected. This differential effect indicates the selective relevance of CD40-CD40L engagement upon monocyte activation by Th1 clones. However, the levels of CD40L expression did not differ in Th1 and Th2 cell clones, implying that additional, unidentified molecule(s) preferentially expressed by Th1 cells are involved due to their capacity to induce IL-1β. Therefore, CD40/CD40L may be a cofactor in the contact-mediated activation of monocytes by stimulated T-lymphocytes. From the knowledge gained to date, CD40-CD40L may be important in terms of quality of stimulation, but it is not crucial. In the author′s system LAG-3 did not induce the production of IL-1β and TNF-α. Others found soluble CD23 induced cytokine production on monocytes [26, 27]. LFA-1 (CD11a/CD18) and CD69 contribute to the activation of human monocytic cells by stimulated T-cells [4, 28]. This was substantiated by a study showing that IL-15 induced synovial T-cells from rheumatoid arthritis patients to activate the production of TNF-α by monocytes. This effect was inhibited by antibodies to CD69, LFA-1 and ICAM-1 [20].

Together these studies suggest that some known surface molecules are involved in T-cell signalling of monocytes. However, inhibitors (*e.g.* antibodies) of these molecules fail to abolish monocyte activation altogether, suggesting that the factor(s) required for T-cell signalling of human monocytes by direct contact remain(s) to be identified. Furthermore, hierarchy and the sequence of events during this crosstalk need to be established.

Identification of a plasma inhibitor of T-cell contact-mediated activation of monocyte-macrophages

The inhibition of T-cell signalling of monocytes may be important in that it would maintain a low level of monocyte activation within the bloodstream. After several steps of purification, apolipoprotein (apo) A-I was identified as being an inhibitor of contact-mediated activation of monocytes. Apo A-I appears to bind preferentially to stimulated T-lymphocytes in this context [29]. These results were further confirmed by using recombinant apo A-I [30]. Apo A-I is a "negative acute-phase protein" and the principal protein of high-density lipoproteins (HDL). Variations of apo A-I concentration were observed in several inflammatory diseases including rheumatoid arthritis [31], and antibodies to apo A-I have been described in serum of patients with systemic lupus erythematosus [32]. Low levels of apo A-I in patients with chronic inflammatory diseases may be a link between infection and chronic inflammation [33].

The identification of HDL-associated apo A-I ligand(s) on stimulated T-cells may lead to the elucidation of the mechanisms and molecules involved in T-cell signalling of monocytes. HDL-associated apo A-I has been shown to bind specifically to a number of cell-surface molecules [34] including HDL-binding protein, scavenger receptor B1, HB2, cubillin, adenosine triphosphate-binding cassette A1 transporter, and a 95 kD protein at the surface of human foetal hepatocytes. All these proteins have a high molecular weight ($\geqslant$80 kD) and to date have not been identified on T-cells. Thus, there is no easy answer as to the identity of the apo A-I ligand at the surface of stimulated T-cells, although a specific HDL-binding site on human T-lymphocytes has been reported but not identified [35, 36]. Furthermore, none of the identified apo A-I ligands display characteristics compatible with the preliminary characterisation of the surface-activating factor on stimulated T-cells, particularly its molecular weight of ~40 kD.

Direct contact of T-lymphocytes with human lung tissue macrophages and alveolar macrophages

Human alveolar macrophages (AM) and lung tissue macrophages (LTM) have a distinct localisation in the

cellular environment. Their response to direct contact with activated T-lymphocytes was studied in terms of the production of interstitial collagenase (MMP-1), 92 kD gelatinase (MMP-9), and TIMP-1, one of the counter-regulatory tissue inhibitors of metalloproteinases [37]. Either AM obtained by bronchoalveolar lavage or LTM obtained by mincing and digestion of lung tissue were exposed for 48 h to plasma membranes of T-lymphocytes previously activated with PMA and PHA for 24 h. In LTM exclusively, but not in AM, membranes of activated T-cells strongly induced the production of MMP-1, MMP-9, and TIMP-1 whereas membranes from unstimulated T-cells failed to induce the release of MMPs (table 1). Both populations of mononuclear phagocytes spontaneously released only small amounts of MMPs and TIMP-1. Similar results were obtained when MMP and TIMP-1 expression were analysed at pretranslational and biosynthetic levels, respectively. Blockade experiments with cytokine antagonists revealed the involvement of T-cell membrane-associated IL-1 and TNF-α on MMP production by LTM upon contact with T-cells. These data suggest that the ability of lung macrophages to produce MMPs after direct contact with activated T-cells is related to the difference in phenotype of mononuclear phagocytes and cell localisation. In addition, these observations indicate that cell-cell contact represents an important biological mechanism in potentiating the inflammatory response of mononuclear phagocytes in the lung. Recently, HDL-apo A-I was observed to interfere with the contact between T-lymphocytes and lung macrophages (fig. 1).

Table 1. – Contact of T-lymphocytes with monocyte-macrophages (MØ) in human lung cells

	Tissue lung MØ	Alveolar lung MØ
MMP-1	+	0
MMP-9	+++	+
TIMP-1	+	+
TNF-α	+++	+++

MMP: matrix metalloproteinase; TIMP: tissue inhibitor of metalloproteinases; TNF: tumour necrosis factor. Crosses indicate the degree of stimulation.

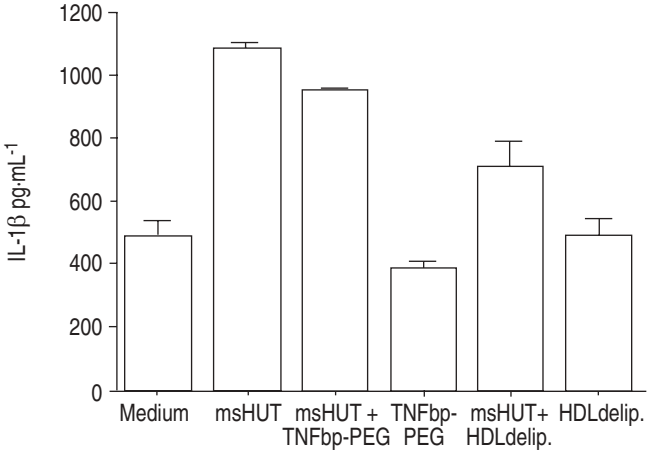

Fig. 1. – Lung tissue macrophages were incubated with medium alone, membrane preparation of stimulated (ms)HUT cell line alone, in the presence of tumour necrosis factor-binding protein-pegylated (TNFbp-PEG) or delipidised high-density lipoprotein (HDLdelip.). Supernatant was tested for interleukin (IL)-1β after 48 h of culture. Values represent mean±SD.

Direct contact between T-lymphocytes and other target cells

Cellular contact with T-lymphocytes induces an imbalance between MMP-1 and TIMP-1 production by dermal fibroblasts and monocytic cells [17] as well as prostaglandin E_2 production by dermal fibroblasts [38]. The T-cell surface molecules involved are mainly IL-1 and TNF-α and not the ligand and counter-ligand involved in T-cell/monocyte interactions. Plasma membranes or fixed, stimulated T-cells markedly inhibited the synthesis of type-I and -III collagen in fibroblasts, whether treated with transforming growth factor-β or not. This inhibition of extracellular matrix production mediated by T-cell contact was partially due to cumulative effects of T-cell membrane-associated IFN-γ, TNF-α and IL-1β [39]. Thus, direct contact with stimulated T-cells favours extracellular matrix catabolism by enhancing MMP production while diminishing collagen synthesis and decreasing the repair process.

The author′s group has demonstrated that membranes of stimulated T-lymphocytes induce the expression of ICAM-1, vascular cell adhesion molecule-1, and E-selectin on microvascular endothelial cells from human brain (HB-MVEC). In addition to cell adhesion molecules, contact-mediated activation of HB-MVEC induced the production of IL-6 and IL-8. Cell contact-induced expression of cell adhesion molecules and the production of IL-6 and IL-8 were inhibited by TNF-α inhibitors demonstrating that membrane-associated TNF-α was largely responsible for the activation of endothelial cells [40].

At an early stage of inflammation T-lymphocytes may also be present simultaneously with PMN in the tissue. PMN produce reactive oxygen radicals, a large variety of proteolytic enzymes and various cytokines, especially IL-8 and IL-1Ra. PMN oxidative metabolism leads to the production of highly reactive oxygen species and contributes to the elimination of pathogenic microorganisms, but it could be harmful to host tissue at the site of inflammation, by causing membrane lipid peroxidation leading to both cell and tissue damage. In previous studies, cellular contact with activated T-cells was shown to stimulate and prime neutrophil oxygen-dependent respiratory bursts [41] and this activity on PMN correlated with that on THP-1 cells, suggesting that similar factors at the surface of stimulated T-cells were involved in the activation of neutrophils and monocytes [5]. The author′s laboratory recently confirmed this and demonstrated that HDL inhibited T-cell contact-induced respiratory bursts in neutrophils [42]. This strongly suggests that analogous molecules at the surface of T-cells are involved in the activation of both monocytes and neutrophils. However, lipid-free apo A-I, but not HDL, proved to inhibit immunoglobulin G-induced superoxide production by PMN [43], hinting at a specific inhibitory activity of HDL to the contact-mediated activation of PMN.

Conclusion

The administration of biologics and biological inhibitors is common practice in medicine, and the use of cytokine antagonists, whether antagonists to ligand binding or to the receptor, has been more successful than the administration of cytokines with inhibitory properties. Of interest, in the human therapeutic arsenal, it is substances acting at the ligand-receptor level that are the most specific. As far as the persistence of inflammation is concerned, the contact between stimulated cells, either migrating from the blood or resident, is most likely to be a major cause of chronic destructive or

Table 2. – Cellular contact with stimulated T-cells differentially affects various target cells

	Direct cellular contact with stimulated T-cells					
	Monocyte-macrophages		Fibroblasts		PMN	Endothelial cells
Production of	IL-1 ↑ TNF-α ↑	IL-1Ra ↑	MMPs ↑ PGE_2 ↑	Collagen	ROS ↑	CAMs IL-6 and IL-8 ↑
Inhibited/reversed by						
IL-1Ra	No	No	Yes	Yes	No	
TNFsR	No	No	Yes	Yes	No	Yes
Anti-IFN-γ	No	No	No	Yes		
HDL-associated apo A-I	Yes	Yes/No	No		Yes	

PMN: polymorphonuclear neutrophils; IL: interleukin; IL-1Ra: interleukin-1 receptor antagonist; TNF: tumour necrosis factor; MMP: matrix metalloproteinase; PG: prostaglandin; ROS: reactive oxygen species; CAMs: cell adhesion molecules; TNFsR: tumour necrosis factor soluble receptor; IFN: interferon; HDL: high-density lipoprotein; apo A-I: apolipoprotein A-I.

fibrotic manifestations. According to a body of evidence, contact between stimulated T-cells and monocytes or mesenchymal cells, which regulate the production of IL-1, TNF, MMP and eicosanoid-derived metabolites, can be inhibited by numerous antibodies to either ligands or counter-ligands, but other plasma components such as HDL apo A-I can also inhibit cell-cell interaction either in the blood stream or by diffusing in the inflamed tissue. This mechanism of control affords a new link and approach between cytokines (*i.e.* IL-1 and TNF production), lipid metabolism and acute-phase proteins. Contact between T-lymphocytes and fibroblasts can also affect collagen synthesis, and the response of the fibroblasts may be strongly dependent on membrane-associated cytokines (*i.e.* IL-1, TNF), which does not apply to the contact between T-lymphocytes and monocytes.

A major goal in the future will probably be to gain more insight into the agents controlling the regulation of ligands and counterligands expressed during cell-cell contact, which clearly varies from one cell to another (table 2).

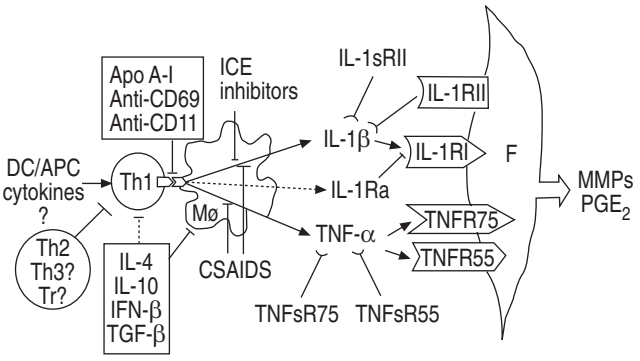

Fig. 2. – Possible interference in the interaction between T-lymphocytes and monocytes. DC: dentritic cells; APC: antigen-presenting cells; Th: T-helper cell; apo A-I: apolipoprotein A-I; IL: interleukin; IFN: interferon; TGF: transforming growth factor; ICE: IL-1β-converting enzyme; Mø: monocyte-macrophages; CSAIDS: cytokine-suppressive anti-inflammatory drugs; TNF: tumour necrosis factor; sR: soluble receptor; R: receptor; F: fibroblast; MMP: matrix metalloproteinase; PG: prostaglandin.

A new approach in therapeutic intervention in chronic inflammatory diseases

One of the hallmarks of chronic inflammatory diseases affecting many organs (*e.g.* lung, joints, kidney) is the persistent contact between stimulated immune cells migrating from the blood stream (*i.e.* T-lymphocytes and monocyte-macrophages) to the organ-specific resident cells (*i.e.* fibroblast-like cells in the lung or the synovium). This contact leads to the production of large amounts of proinflammatory cytokines (*i.e.* IL-1 and TNF), which induce the production of proteases that contribute to the destruction of the matrix (*i.e.* collagen, proteoglycans). Simultaneously, the new synthesis of matrix components is either decreased (lack of repair process) or, on the contrary, abnormally increased (fibrosis), entailing the loss of normal functions. Previous successful therapeutic advances have consisted of blocking the action of IL-1 and/or TNF.

The author's new approach is based on impeding the production of both interleukin-1 and tumour necrosis factor during the contact between T-lymphocytes and monocytes. This will hopefully be achieved after elucidating the cell-surface molecules involved in this cell-cell contact and investigating the natural soluble molecule(s) that can prevent this contact. Indeed, it was found that lipoprotein such as high-density lipoprotein/apolipoprotein A-I is a potent inhibitor of this cell-cell contact. This is of particular interest in that high-density lipoprotein/apolipoprotein A-I is considered to be a beneficial component of lipid metabolism and apolipoprotein A-I a negative acute-phase protein, which unfortunately decreases during inflammation and therefore leads to the lack of inhibition during cell-cell contact. This new concept bridges the gap between inflammation, lipid metabolism, acute-phase proteins and other diseases such as arteriosclerosis (fig. 2).

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