Intracellular Signaling Mechanisms Underlying the Expression of Pro-inflammatory Mediators in Airway Diseases

Chuen-Mao Yang[1,2], PhD; Hsi-Lung Hsieh[2], PhD; Chiang-Wen Lee[2], MS


Prof. Chuen-Mao Yang

Several factors have been shown to trigger the pathogenesis of asthma and airway inflammation mechanisms. Elevated levels of pro-inflammatory cytokines including tumor necrosis factor-α and interleukin-1β in the bronchoalveolar lavage fluid have been detected in asthmatic patients. Cytokines exert as potent stimuli in inflammatory responses through up-regulation of many gene expressions, including cytokines, chemokines, cytosolic phospholipase A_2, cyclooxygenase, adhesion molecules and matrix metalloproteinases. The extent of these gene expressions is correlated with the severity of inflammation. However, the intracellular signaling mechanisms underlying the expression of target proteins regulated by these factors are elusive. The mechanisms underlying actions by cytokines may be integrated to the signaling networks that augment airway inflammation by recruiting leukocytes and leading to airway remodeling. Although cytokines have been reported to activate mitogen-activated protein kinases including p42/p44 and p38, and c-Jun N-terminal kinase, the relationship between the activation of these pathways and expression of inflammatory genes remains unknown. Moreover, many genes regulated by mitogen-activated protein kinases are dependent on NF-κB for transcription. NF-κB has also been shown to be involved in target protein expression at the transcriptional level in various cell types. We review the mechanisms underlying the intracellular signaling involved in several target protein expressions induced by cytokines in airway resident cells. Conclusion: Increased understanding of signal transduction mechanisms underlying target protein gene expression will create opportunities for the development of anti-inflammation therapeutic strategies. *(Chang Gung Med J 2005;28:813-23)*

Key words: interleukin-1β, tumor necrosis factor-α, cyclooxygenase-2, cytosolic phospholipase A_2, prostaglandin E_2, MAPKs, NF-κB, adhesion molecules, matrix metalloproteinases.

Airway inflammation is central to the pathogenesis of asthma and other airway diseases, such as chronic obstructive pulmonary disease. In the last decade, several citations have suggested that inflammatory processes that underlie airway diseases are regulated by a network of mutually interacting cytokines. Elevated levels of pro-inflammatory cytokines including tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) in the bronchoalveolar lavage fluid have been detected in allergic asthmatic patients.[1,2] Recent evidence suggests that cytokine-induced changes in the airway's smooth muscle phe-

From the [1]Graduate Institute of Natural Products; [2]Department of Physiology and Pharmacology, Chang Gung University, Taoyuan.
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Correspondence to: Prof. Chuen-Mao Yang, Department of Physiology and Pharmacology, Chang Gung University. 259, Wen-Hwa 1st Rd., Gueishan Shiang, Taoyuan, Taiwan 333, R.O.C. Tel.: 886-3-2118800 ext. 5123; Fax: 886-3-2118365; E-mail: chuen-mao@mail.cgu.edu.tw

notype may modulate bronchial hyper-responsiveness and airway inflammation.[3] In previous years, our group has demonstrated that TNF-α and IL-1β may trigger some intracellular signaling pathways to regulate many inflammatory gene expressions in airway resident cells, including human/canine airway smooth muscle cells (ASMCs) and human lung epithelial cell line A549.

Cytokines present in the airways clearly regulate both the initiation and maintenance of immune and inflammatory responses. They are secreted by a variety of cells including monocytes and macrophages that respond to virus infection, activated by lymphocyte products, microbial toxins and other stimuli.[4] Several studies have demonstrated that TNF-α and IL-1β are the most potent cytokines and exert influence on a wide range of biological activities in airway inflammatory diseases including asthma and bronchiotitis.[5-10] Moreover, there is increasing evidence that TNF-α and IL-1β are directly linked to airway inflammation and hyper-responsiveness observed in asthma. ASMCs are one of important effector cells in asthma. Previous studies have demonstrated that ASMCs are multifunctional, having the capacity for contraction, migration and proliferation, and synthesis of extracellular matrix (ECM), growth factors, cytokines, chemokines and matrix metalloproteinases (MMPs).[11,12] For example, human TNF-α is synthesized as a pro-protein comprising 233 amino acids, with a molecular mass of 26 kDa. The pro-protein is cleaved by a specific metalloprotease (also named TNF-α converting enzyme, TACE) to yield a monomeric form of 17 kDa comprising 157 nonglycosylated amino acids.[13] The pleiotropic actions of TNF-α range from proliferative responses, such as cell growth and differentiation, to host defense effects, such as inflammation and autoimmunity, and to destructive cellular outcomes, including apoptotic and necrotic cell death mechanisms.[14] By contrast, IL-1 is a family of proteins. IL-1α and β are believed to exert identical actions through a single receptor (IL-1RI), which requires an accessory protein (AcP) for signal transduction. A third member of the family, IL-1 receptor antagonist (IL-γa), acts as a highly selective, competitive antagonist, which appears to block all actions of IL-1 but has no identified independent actions.[15] All three IL-1 molecules are formed as precursors: pro-IL-1α and pro-IL-1ra are biologically active but pro-IL-1β is inactive. Cleavage and release of active IL-1β from cells is catalyzed by caspase-1, one of a family of enzymes that are central mediators of apoptosis.[16] On the basis of our studies, TNF-α and IL-1β exert similar responses, mediated through common mechanisms, in airway inflammation. We and others have found that ASMCs have a highly increasing level of inflammatory proteins induced by TNF-α or IL-1β. These inflammatory-corresponding proteins include cytosolic phospholipase A_2 (cPLA_2), cyclooxygenase (COX)-2, adhesion molecules, chemokines and proteases.[4,6,17-19] Furthermore, the cellular and molecular mechanisms regulating the expression of inflammatory genes in ASMCs by cytokines will probably lead to new therapeutic approaches in the management of asthma. In our previous studies, there are, at least in part, several signaling pathways involved in the regulation of the expression of inflammatory genes in ASMCs and A549 cell line.[4,17,19-22] These mechanisms involve JNK, ERK, p38 MAPK, PKC, calcium and Src/EGFR/PI3K/Akt transactivation pathways and lead to activation of transcription factors such as NF-κB and AP-1. This review, giving an understanding of the contributions of cytokines to ASMCs and A549 cell line linked with airway inflammation, may therefore provide a new insight into the pathogenesis of respiratory diseases.

Roles of COX-2 and PGE_2 in airway inflammatory diseases

We and others have demonstrated that human or canine ASMCs express COX-2 upon stimulation by a variety of pro-inflammatory cytokines such as TNF-α, IL-1β and other mediators[4,17,19,20,23] and release a large amount of prostanoids, mainly prostaglandin E_2 (PGE_2). Prostaglandins (PGs) play important roles in many biological processes, which in turn, in an autocrine manner, modulate the cell functions such as proliferation, relaxation and the synthesis of growth factors. Altered prostanoid production is associated with a variety of illnesses, including acute and chronic inflammation, cardiovascular disease, colon cancer and allergic diseases.[24] COX is the rate-limiting enzyme for the conversion of arachidonic acid to prostanoids and exists in two isoforms: COX-1 is constitutively expressed and is homeostatic in function as the housekeeping form; in contrast, COX-2 is associated with inflammation and

is induced in response to mitogenic and proinflammatory stimuli. The expression of COX-2 is a key element in various pathophysiological processes, including inflammation,[25] cardiovascular disease,[26] tissue remodeling[27] and cancer.[28] In contrast, COX-2 is recognized as mediating inflammatory responses and is highly restricted under basal conditions but is rapidly induced by pro-inflammatory cytokines.[29] In our studies, the MAPK and NF-κB pathways play key roles in regulation of COX-2 expression and PGE_2 production in human or canine ASMCs.[4,17,19,20] Pretreatment with several pharmacological inhibitors of MEK1/2 (PD98059), p38 MAPK (SB202190), tyrosine kinase (genistein), phosphatidylcholine-specific phospholipase C (PC-PLC) (D-609) and PKC (GF109203X), attenuated TNF-α or IL-1β-induced COX-2 expression and PGE_2 synthesis in TSMCs. TNF-α- or IL-1β-induced COX-2 expression and PGE_2 synthesis are also inhibited by a selective NF-κB inhibitor pyrrolidine dithiocarbamate (PDTC). These findings suggest that the increased expression of COX-2 correlates with the release of PGE_2 from TNF-α- or IL-1β-challenged TSMCs, at least in part, mediated through p42/p44 and p38 MAPKs as well as NF-κB signaling pathways. In addition, PKC-dependent tyrosine kinase activation is also involved in TNF-α-induced NF-κB activation and COX-2 expression in NCI-H292 alveolar epithelial cells.[30,31] Several bacterial products such lipoteichoic acid (LTA), a major component of the gram-positive bacterial cell wall, and lipopolysaccharide (LPS), a major component of the gram-negative bacterial cell wall, and pro-inflammatory mediator bradykinin (BK) also induce COX-2 expression and PGE_2 synthesis via similar signaling pathways in human lung epithelial cell line A549.[32,33] Moreover, COX-2 protein expression is regulated by PI3K/Akt pathway in A549 cell line.[34,35] In our previous studies, the results show that LPS stimulates COX-2 up-regulation in canine ASMCs.[19] It has been shown that activation of macrophages by LPS is mediated by LPS-binding protein, which transfers LPS to its cellular receptor consisting of CD14, Toll-like receptor 4 (TLR4) and the MD-2 molecule in several cell types.[36-39] Further, we first show that in HTSMCs, LTA triggers activation of p42/p44 MAPK pathway, mediated through a TLR2 receptor.[40] It remains unclear, however, whether LTA elicits signaling through TLR2 for COX-2 expression in airway resident cells. Taken together, these results indicate that the role of COX-2-derived PGE_2 synthesis might play a pivotal role in airway inflammation diseases.

Role of $cPLA_2$ in airway inflammatory diseases

Mammalian cells contain structurally diverse forms of PLA_2 including secretory PLA_2 ($sPLA_2$), calcium-independent PLA_2 ($iPLA_2$) and the novel, high molecular weight (85 kDa) $cPLA_2$.[41] $cPLA_2$ is the major intracellular form of PLA_2, which preferentially hydrolyzes membrane phospholipids at the *sn*-2 position to release arachidonic acid and represents the rate-limiting enzyme in eicosanoid production. $cPLA_2$ is a widely distributed enzyme and the transcript is expressed at a fairly constant level in all human tissues with somewhat elevated levels in the lung and hippocampus.[41-43] The increase in $cPLA_2$ activation and expression following external stimuli, including pro-inflammatory cytokines, growth factors and oxidants, is often observed in several systems.[44,45] The $cPLA_2$ promoter has been isolated from both human[46,47] and rat,[48] which contains a number of putative regulatory elements including AP-1 sites, NF-κB sites and glucocorticoid regulatory elements. Previous studies have reported that the c-Jun N-terminal kinases (JNK) and ERK pathways are necessary for induction of $cPLA_2$ in lung epithelial cells and non-small cell lung cancer. Activation of JNK, ERK and Ras pathways leads to induction of c-Jun protein, which showed functional cooperation with Sp1 in driving $cPLA_2$ promoter activity.[49] In addition, regulation of $cPLA_2$ by phosphorylation is related to released arachidonic acid. Activation of different MAPK cascades, including p42/44 MAP kinase (ERK1/2), p38 MAPK and/or JNK, can directly phosphorylate at Ser^{505} and Ser^{727} on $cPLA_2$ and has been described in several cell types.[50-53] Previous studies have shown that PMA, a PKC activator, induces $cPLA_2$ α expression in various cell types including human bronchial epithelial cells.[54,55] Moreover, activation of $cPLA_2$ by epidermal growth factor (EGF) and calcium ionophore (A23187) results in increasing IL-8 and COX-2 reporter gene activity in A549 cell line.[56] However, it remains unclear whether $cPLA_2$ expression and activation in ASMCs by inflammatory mediators, such as cytokines, bacterial products and BK, may influence COX-2 protein expression and PGE_2 synthesis.

Role of adhesion molecules in airway inflammatory diseases

Leukocytes continuously circulate throughout the body in order to come into contact with antigens sequestered within tissues. To enter tissues, circulating leukocytes migrate from the blood, between vascular endothelial cells and into the tissue. During this migration, leukocytes initially bind to endothelial cells via low affinity adhesion molecules. The low affinity adhesion in combination with the force of the blood flow results in the rolling of leukocytes on endothelial cells. Subsequently, adhesion molecule affinity is up-regulated and leukocytes firmly adhere to the endothelium.[57,58] Finally, bound leukocytes migrate between the endothelial cells and into the tissue. Vascular cell adhesion molecule-1 (VCAM-1 CD106) is one of the inducible cell transmembrane glycoproteins of the immunoglobulin supergene family expressed in several cell types, and plays an important role in a number of inflammatory and immune responses.[59,60] VCAM-1 structure and binding functions have been characterized. It binds to $\alpha_4\beta_1$ (Very Late Antigen-1; VLA-4; CD49d/CD29) or $\alpha_4\beta_7$ integrins on leukocytes. It was first identified as an adhesion molecule induced in endothelial cells by inflammatory cytokines (IL-1β and TNF-α) or LPS.[61,62] Up-regulation of VCAM-1 expression in cytokine-triggered vascular endothelial cells enhances the targeted transmigration of polymorphonuclear leukocytes (PMNs) into the extravascular space of inflammation.[63] We and others have demonstrated that induction of VCAM-1 is regulated by inflammatory cytokines such as IL-1β, TNF-α, and IFN-γ on human umbilical vein endothelial cells, pulmonary artery endothelial cells,[64] intestinal epithelial cells,[65] keratocytes,[66] renal tubular epithelial cells,[67] pulmonary epithelial cells A549,[21] and human ASMCs.[22] The other important adhesion molecule is the intercellular adhesion molecule-1 (ICAM-1 CD54). In a number of inflammation and immune responses, ICAM-1 binds to two integrins belong to the β_2 subfamily, LFA-1 and Mac-1, both are expressed by leukocytes and promote the adhesion and transendothelial migration of leukocytes. Basal levels of ICAM-1 are low but high expression also can be induced in a number of cell types by a wide range of ligands, including LPS, phorbol esters and inflammatory cytokines such as IL-1β and TNF-α.[68,69] In normal processes, the adhesion molecule is important during development since VCAM-1 knockout is lethal to embryonic development. However, in pathogenesis, adhesion molecule expression is induced on endothelial cells during inflammatory bowel disease, atherosclerosis, infection and asthmatic responses. In airways, to reach the submucosa and airway lumen, circulating PMNs must first be recruited across the vascular endothelium and then migrate through the interstitial matrix before interacting with the airway epithelium.[70,71] In the pathogenesis of asthma, eosinophil migration into the lung is adhesion molecule dependent.[72,73] Accumulation of inflammatory cells within the airways can be influenced by expression of adhesion molecules on airway epithelium. Thus, similar processes that govern PMN adhesion to lung airway resident cells may occur and contribute to the damage to these cells seen in asthma inflammatory responses.[74,75] This event is crucial in the development of allergic inflammation and is mediated by adhesion molecules and cytokines.[76-78] During these interactions, PMNs and lung tissue undergo cytokine-specific up-regulation of adhesion molecules.[79] Several reports have described that ICAM-1 or VCAM-1 expression induced by pro-inflammatory cytokines may be mediated through a number of MAPKs, the transcription factor NF-κB and AP-1.[80-85] The regulation of NF-κB by cytokines is an example of a signaling pathway which is fundamentally important in inflammatory diseases. NF-κB activation requires phosphorylation-dependent degradation of the κB protein inhibitor (IκB), which sequesters NF-κB in the cytoplasm. This step is mediated via a multiprotein IκB kinase (IKK) complex consisting of two catalytic subunits, IKKα and IKKβ, and a regulatory subunit, IKKγ, which is in turn activated by receptor inactivating protein (RIP). Through this pathway, cytokines target IκB to the proteosome for ubiquitination and stimulate translocation of NF-κB into the nucleus.[86-88] However, there is a difference between our studies and others: in A549 cells, activation of p42/p44 MAPK and JNK cascades, at least in part, mediated through NF-κB pathway is essential for IL-1β induced ICAM-1 gene expression;[21] others mention that Src activation by PKC mediated through NF-κB pathway is essential for IL-1β- or TNF-α-induced ICAM-1 but not p44/42 MAPK, p38 and JNK pathways.[89] In addition, our findings also show that IL-1β or TNF-α-induced VCAM-1 expres-

sion is mediated by the NF-κB pathway based on the early nuclear NF-κB translocation but activation of NF-κB is independent on p44/42 MAPK, p38 and JNK pathways. However, activation of p44/42 MAPK, p38 and JNK is also involved in IL-1β or TNF-α-induced VCAM-1 expression in human ASMCs.[22] Furthermore, clarifying that the mechanisms underlying the expression of adhesion molecules in airway resident cells may be candidate targets for therapeutic intervention in certain conditions of airway inflammation.

Role of MMPs in airway inflammatory diseases

Airway remodeling, a key feature of persistent asthma, is also characterized by the deposition of ECM proteins in the airways.[90,91] Matrix metalloproteinases (MMPs) are a family of ECM-degrading enzymes and are induced by different stimuli including growth factors, cytokines and tumor promoters. MMPs play important roles in inflammation, tissue remodeling, angiogenesis, wound healing, tumor invasion and metastatic progression.[92-94] MMP-9 (gelatinase B, 92-kD type IV collagenase) is one of two MMPs referred to as gelatinases and released from cells as a proenzyme. The other is MMP-2 (gelatinase A, 72-kD type IV collagenase). MMP-9 cDNA was first cloned from transformed human fibroblasts.[95] The MMP-9 gene is on human chromosome 20q11.1-13.1, a position associated with bronchial hyper-responsiveness.[96] More than 100 articles have shown that MMP-9 is present at low quantities in the healthy adult lung but much more abundantly in several lung diseases, including asthma and chronic obstructive pulmonary disease.[97] Recent evidence also suggests that MMP-9 is induced during airway inflammation.[98] In the normal lung, MMP-9 is not produced by resident cells but under various forms of stimulation, bronchial epithelial cells,[99] alveolar type II cells,[100] ASMCs[101] and endothelial cells[102] produce MMP-9. Although several lines of evidence have proved that MMP-9 plays a critical role in airway inflammation, the mechanisms involving this enzyme in inflammatory responses are still unclear. Pro-inflammatory cytokines such as TNF-α and IL-1β stimulate MMP-9 production in many cell types.[103,104] It has been demonstrated that cytokines exert their effects via transcription factors such as AP-1 and NF-κB. The MMP-9 promoter in a 2-kb 5' flanking region contains AP-1, AP-2, SP-1 and NF-κB transcription factor binding sites. Several studies have shown that a conserved proximal AP-1 binding site is required for the induction of MMP-9,[105-107] and analysis of the MMP-9 promoter has identified an essential proximal AP-1 element and an upstream NF-κB site.[108] Recently, our studies have shown that MMP-9 is also involved in brain injury. MMP-9 up-regulation is stimulated by cytokines and BK in rat brain astrocyte-1.[109,110] IL-1β- and BK-induced MMP-9 mRNA and protein expression are attenuated by inhibitors of MEK1/2 (PD98059), p38 (SB20190), JNK (SP600125), PI3-K (LY294002) and NF-κB (helenalin). In accordance with these findings, phosphorylation of p42/p44 MAPK, p38, JNK and Akt, and activation of NF-κB are attenuated by prior treatment with PD98059, SB202190, SP600125, LY294002 and helenalin, respectively.[109,110] These results indicate that MMP-9 expression is regulated by MAPKs, PI3K/Akt and NF-κB pathways in RBA cell line. In vivo, MMP-9 is likely activated via a protease cascade. The pro-domain (~10 kDa) can be cleaved by other proteases such as MMP-2, MMP-3 and MT1-MMP.[94] We have found that up-regulation of MMP-9 associated with cell migration is significantly attenuated by both GM6001 (inhibitor of MT1-MMP) and MMP-9 antibody in human limbal epithelial cells.[111] However, the mechanisms of MMP-9 expression and activation in airway resident cells mediated through a similar signaling pathway as RBA-1 cells and human limbal epithelial cells need to be further investigated.

Conclusion

In recent years, the signaling pathways regulating ASM growth, gene expression and protein synthesis have been elucidated, and are summarized in Figure 1. Binding of cytokines to their receptors results in activation of p42/p44 MAPK, p38, JNK and NF-κB pathways. These signaling pathways may converge at some points and contribute to sustained activation of transcription factors required for inflammatory gene expression. For example, the MAPKs and PI3K/Akt signaling pathways appear to constitute the major pathways required for cell survival, proliferation and gene expression in both immune and non-immune cells (airway epithelium, ASM and lung parenchymal cells). Moreover, the transcription factor NF-κB is also an important sig-

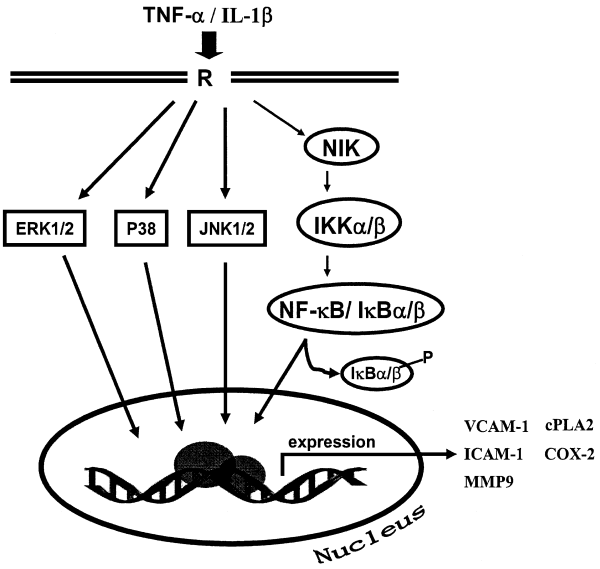

Fig. 1 Schematic Representation of Signaling Pathways Involved in TNF-α or IL-1β-induced Inflammatory Gene Expression.
Binding of cytokines to their receptors results in activation of p42/p44 MAPK, p38, JNK and NF-κB pathways. These signaling pathways may converge at some points and contribute to sustained activation of transcription factors required for inflammatory gene expression.

naling module for synthesis of many of the mediators such as cytokines (IL-1 and TNF-α) and adhesion molecules (ICAM-1 and VCAM-1) in the processes of chronic airways diseases such as asthma. Elucidation of various signal transductions and the molecular mechanisms regulating ASM gene expression may provide insight into the therapeutic strategies of airway diseases and designing of new anti-inflammatory drugs for treating asthma.

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呼吸道疾病中前發炎物質生成的細胞內訊息傳遞機制

楊春茂[1,2] 謝喜龍[1] 李江文[1]

氣喘及呼吸道疾病的病理機制已經知道是由一些因子的誘發所形成。在患有氣喘病病人的支氣管抽出液中可以偵測到大量與發炎相關的細胞激素因子，包括了腫瘤壞死因子 (TNF) 與介白素 (IL-1)。細胞激素群可以藉由刺激細胞引發許多發炎相關基因的表現，例如細胞激素本身，化學趨化物，細胞磷脂酶 A2，環氧化酶，黏著分子及金屬蛋白分解酶。這些基因的表現與嚴重的發炎反應有著密切的相關性。然而，藉由發炎因子來調控發炎基因的細胞內訊息傳遞機制已經被清楚的闡述。由細胞激素群作用之下所整合成的訊息網絡會導致大量白血球的聚集及呼吸道的重建，最終引發呼吸道的嚴重發炎。雖然細胞激素已經知道會活化分裂原活性蛋白激酶 (MAPK)，包含 p42/p44 MAPK，p38 及 JNK，可是這些激酶之間的關係卻仍未清楚。再者，分裂原活性蛋白激酶在基因的調控過程中必須依靠細胞核轉錄因子 (NF-κB) 的作用來達到基因的轉錄。細胞核轉錄因子 (NF-κB) 已被證實參與許多不同細胞內蛋白質的轉錄過程中。因此，本篇文獻將回顧呼吸道細胞中，細胞激素藉由一連串的細胞內訊號傳遞機轉所調控發炎相關蛋白質的表現。增加對細胞內訊號傳遞機轉的了解，期望可以帶來更多抗發炎治療的新策略。(長庚醫誌 2005;28:813-23)

關鍵字: 介白素-1β，腫瘤壞死因子-α，環氧化酶-2，細胞磷脂酶A2，前列腺素E2，分裂原活性蛋白激酶，NF-κB，黏著分子，金屬蛋白分解酶。

[1]長庚大學醫學院生理暨藥理學科，[2]天然藥物研究所
受文日期：民國94年4月28日；接受刊載：民國94年8月17日
通訊作者：楊春茂教授，長庚大學　醫學院　天然藥物研究所。桃園縣333龜山鄉文化一路259號。Tel.: (03)2118800轉5123; Fax: (03)2118365; E-mail: chuenmao@mail.cgu.edu.tw