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Cyperus rotundus L. enhances CD4+ T-cell activities and modulates Th1/Th2 differentiation

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Cyperus rotundus L. (CR) is a common used herbal medicine in Asian countries such as Korea, China and Japan. The present study was designated to evaluate the direct effects of CR on helper T cell activities and on Th1/Th2 lineage development in vitro. The results demonstrated that CR had no mitogenic effects on unstimulated CD4+ T cells, but augmented CD4+ T-cell proliferation upon activation with anti-CD3/anti-CD28 antibodies in a dose-dependent manner. CR treatment significantly increased CD4+ T cell population and the IFN-γ expression was significantly enhanced, while IL-4 expression was significantly decreased. In addition, in vitro Th1/Th2 polarization experiments revealed that CR enhanced IFN-γ secretion in Th1 cells, but reduced the IL-4 in Th2 cells in dose-dependent manner. Conclusions: Therefore, these results suggest that CR treatment could be a desirable alternative therapy for the prevention or correction of Th2 dominant pathological disorders, such as allergy and asthma.

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CT20126, a novel immunosuppressant, prevents collagen-induced arthritis through the down-regulation of inflammatory gene expression by inhibiting NF-kB activation

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Immunesuppressant regulates inflammatory responses and pathogenesis of immune disease, including rheumatoid arthritis. We synthesized a potent and selective immunesuppressive drug (CT20126) and examined the effects of this inhibitor in the settings of inflammation and arthritis. The inhibitor suppressed the expression of inducible nitric oxide synthase (iNOS), tumor necrosis factor-alpha (TNF-a), and interleukin-1 beta (IL-1b) and the production of NO in immune-activated macrophages and osteoblasts as well as LPS-administrated mice. CT20126 suppressed NF-kB activation and iNOS promoter activity by suppressing the inhibitor of IkB kinase (IKK) activity and IkB-a degradation. Furthermore, in vivo administration of CT20126 significantly decreased the incidence and severity of arthritis as well as the expression of iNOS, TNF-a and IL-1b in the paws of collagen-induced arthritic mice compared with controls. These observations indicate that the anti-inflammatory and anti-arthritic effects of CT20126 may be ascribed to the suppression of NF-kB-dependent inflammatory gene expression through the inhibition of IKK activity. Together, these findings reveal that the inhibitory effect of CT20126 on IKK-dependent NF-kB activation may have potential therapeutic value for arthritis and other inflammatory diseases.

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Colchicine-derived compound CT20126 promotes skin allograft survival by regulating the balance of Th1 and Th2 cytokine production

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Colchicine has been shown to regulate the expression of inflammatory gene, but this compound possesses much weaker anti-inflammatory activity. In this study, we synthesized a new colchicine derivative CT20126 and examined its immunomodulatory property. CT20126 was found to have immunosuppressive effects by inhibiting lymphocyte proliferation without cytotoxicity and effectively inhibit the transcriptional expression of the inflammatory genes, inducible nitric oxide synthase, tumor necrosis factor-alpha (TNF-α), and interleukin-1 beta (IL-1β), in macrophages stimulated lipopolysaccharide. This effect was nearly comparable to that of cyclosporine A. This compound also significantly suppressed the production of nitric oxide and Th1-related pro-inflammatory cytokines, IL-1β, TNF-α, and IL-2, with minimal suppression of Th2-related anti-inflammatory cytokines IL-4 and IL-10 in the sponge matrix allograft model. Moreover, administration of CT20126 prolonged the survival of allograft skins from BALB/c mice (H-2d) to the dorsum of C57BL/6 (H-2b) mice. The in vivo immune suppressive effects of CT20126 were similar to that of cyclosporine A. These results indicate that this compound may have potential therapeutic value for transplantation rejection and other inflammatory diseases.

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Chemical reactivity of hydroquinone plays a critical role in its anti-inflammatory action

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Hydroquinone, an environmentally toxic compound, has been suggested to have anti-inflammatory potency. However, its molecular inhibitory mechanism has not been largely unelucidated. In the present study, we report as to how hydroquinone act as a strong negative regulator in the modulation of lipopolysaccharide (LPS)-induced responses of macrophages. Thus, it suppressed the production of nitric oxide (NO) as well as the expression of inducible NO synthase (iNOS) in activated RAW264.7 cells. Hydroquinone clearly blocked the translocation of NF-kB and the activation of signals for the event such as phosphatidylinositol-3 kinase (PI3K)/Akt pathway. Furthermore, the inhibitory mode of action by hydroquione seems to be related to its chemical property. Thus, thiol group-containing compounds such as L-cysteine and dithiothreitol (DTT) remarkably abrogated hydroquione-mediated inhibition. Therefore, our data suggest that hydroquinone may act as a strong negative regulator of macrophage-mediated immune responses via modulating intracellular signaling cascade involved in NF-kB translocation and via mediating the chemical feature of hydroquinone itself. [1]This work was Supported by grants form KRF and KOSEF * corresponding author

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CD98, CD29 and CD 147 are functionally and biochemically associated at adhesion site[1]

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CD29, CD98 and CD147 are known to be functionally important adhesion molecules in various immune cells such as monocytes, macrophages and T cells. Although these three molecules have been reported to be functionally associated, the exact mechanism of inter-regulation was not yet fully elucidated. Surface level of CD29, CD98 and CD147 were found to be highly expressed in monocytic cell line U937 cells. Agonistic antibodies to CD29, CD98 and CD147 also triggered the homotypic cell-cell adhesion of U937 cells. Furthermore, the function-blocking antibodies to CD29, CD98 and CD147 suppressed U937 cell adhesion induced by CD29, CD98 or CD147. Interestingly, these three molecules were co-localized at cell-cell contact site and also associated with rearranged actin cytoskeleton. Similarly, cytochalasin B strongly blocked all cell-cell adhesion events. Finally, we found these CD98 and CD147 were biochemically associated, according to immunoprecipitation and immunoblotting analyses. Therefore, the several lines of evidence suggest that these molecules may coordinate together in regulating immune cell' s migration, adhesion and activation. [1]This work was Supported by grants form KRF and KOSEF * corresponding author

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Burkholderia pseudomallei immunome: a platform to unravel bacterial pathogenesis and vaccine discovery

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Burkholderia pseudomallei, the etiological agent of human and animal melioidosis, remains an enigma in terms of its pathogenic mechanism. We undertook to survey all the B. pseudomallei immunogenic proteins to dissect pathogenesis and evaluate vaccine candidates. A B. pseudomallei genomic expression library was screened with melioidosis patient sera and 109 immuno-reactive clones were identified. Sequence analysis delineated these clones into functional classes of envelope biogenesis, motility and secretion, transcription, amino acid transport and metabolism, inorganic ion transport and metabolism, energy production, protein synthesis, DNA synthesis and metabolism and hypothetical proteins. Complete ORFs of five topologically variable immunogenic proteins were cloned, expressed and shown to maintain immuno-reactivity with melioidosis patient sera. Eighty percent of BALB/c mice immunized with the strongest immunogenic protein, OMA, were protected following challenge with B. pseudomallei D286. Mouse anti-OMA polyclonal sera confirmed the presence of wild type OMA in B. pseudomallei crude lysate. Protein sequence analysis revealed that OMA is a member of the Omp85 family and is highly conserved among species within the Burkholderia genus, suggesting its suitability as a universal vaccine or diagnostic epitope for Burkholderia sp. In addition we also propose the utility of Omp85 as a potential prophylactic agent for melioidosis. Identifying the B. pseudomallei immunome has shed new light on unraveling the bacterium' s pathogenic mechanism and disease severity. These immunogens can be further evaluated as vaccine and sero-diagnostic candidates as well as drug targets. [Supported by MOSTI, Malaysia:IRPA Grant 09-02-02-002(BTK/TD/003)]