

Delayed Type Hypersensitivity

Introduction

Delayed type hypersensitivity (DTH), also known as cell mediated immune memory response or type IV hypersensitivity is characterized by erythema and induration at the site of contact in sensitized humans or animals. It is involved in the pathogenesis of many infectious diseases (tuberculosis, leprosy, blastomycosis, histoplasmosis, toxoplasmosis, leishmaniasis, etc.), autoimmune diseases and granuloma due to infection of foreign antigens. Another form of DTH is the contact dermatitis caused by poison ivy, chemicals or heavy metals, etc. Systemic injection of an antigen in an animal results in fever, synthesis of acute phase proteins and death in some instances. The histology of DTH can be different for different species, but in general it is characterized with an influx of immune cells at the site of injection, either macrophages and basophils in human and mice or neutrophils in guinea pigs and induration which becomes apparent within 24-72 hours. T cells (either CD4+ or CD8+ depending on the antigen) are required to initiate the reaction even though they make up only a small fraction (10-20%) of the inflammatory infiltrates. Cytokines secreted by helper T cells (monocyte chemotactic factor, interleukin-2, interferon γ , TNF α / β) represent the early hallmarks of the inflammation. However, it remains unclear whether the recruitment of other immune cells to the site of challenge is directly regulated by T cells.



PharmaLegacy Models and Research Tools

DTH Rodent Models:

- * Dinitrofluorobenzene (DNFB) induced DTH in ICR, Swiss, or BALB/c mice (Related to contact dermatitis in human)
- * Oxazolone induced DTH in ICR, Swiss, or BALB/c mice (Related to contact dermatitis in human)
- * Methylated bovine serum albumin (mBSA) induced DTH in C57BL6 mice or SD rats (Related to chronic transplant rejection and multiple sclerosis in human. Sheep red blood cells (SRBC) induced DTH in Swiss mice (Related chronic transplant rejection in human.)

Rodent model characteristics:

- * Peak response at 24-48h, rare erythema and different numbers of lymphocytes/monocytes across different models
- * High throughput and requirement for smaller quantity of compound
- * Low variability between subjects using inbred animals
- * Higher concentration of antigen/hapten for induction in certain strains

Measurement of inflammatory responses and molecular pharmacology:

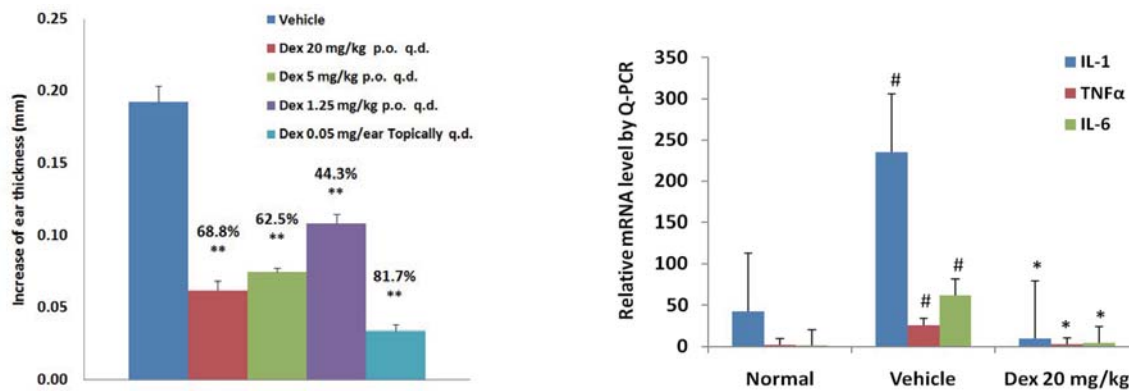
- * Ear/paw swelling
- * Myeloperoxidase assay (neutrophils and granulocytes)
- * Cytokine production: TNF α , interferon γ , IL-1 β , IL-4, IL-6, Cox-2, (ELISA or Q-PCR)

Histopathology:

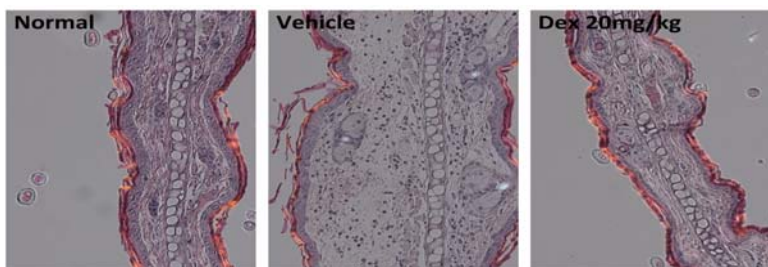
- * H&E staining: induration and infiltrations
- * Immunohistochemistry: specific T cell response and cell proliferation

Case Study - Oxazolone Induced DTH in ICR Mice

Therapeutic effect of Dexamethasone on oxazolone induced DTH in ICR mice:



ICR mice were sensitized with 150 μ l 3% oxazolone topically on day 1 and challenged with 20 μ l 1% oxazolone on day 6. Ear thickness was measured 24 hours after the challenge. The oral treatment with Dexamethasone (daily from day 1 to day 6 and at 6 hours and 23 hours after the challenge, respectively) dose-dependently reduced the increase of ear thickness, while the topical treatment (application on the right ear at 1 hour and 6 hours after the challenge) significantly inhibited the increase of ear thickness. (# $P < 0.05$ vs normal, * $P < 0.05$, ** $P < 0.01$ vs vehicle by Dunnett's multi-comparison test).



H&E staining of the ear tissue showed the ear swelling and infiltration and the inhibitory effect of oral Dexamethasone treatment.

DTH models provide a set of powerful tools for early characterization of immunosuppressor/immunomodulator compounds. The results are often helpful in the profiling of applications of the drug compounds in different immune disease areas. Our expertise with extensive hands-on experience in both immunology and pharmacology have fully validated the various DTH models and can provide you with high quality data for the evaluation of your candidate compounds for the treatment of DTH, early proof-of-concept and the preventive and therapeutic potentials in immune disease and inflammatory disease.

About PharmaLegacy Services

- World-class quality with increased speed and output at competitive cost.
- International GLP and QA-based operation.
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- AAALAC accredited large capacity to house over 10,000 animals under SPF and conventional conditions.
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