THE GRADUATE COLLEGE OF THE
UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

ANNOUNCES THE FINAL EXAMINATION OF

Benjamin Frempah

FOR THE DEFENSE OF THE DOCTOR OF PHILOSOPHY DEGREE
GRADUATE COLLEGE
Graduate Pharmaceutical Sciences

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College of Pharmacy, Room 339

THE ROLE OF IL-6Rα IN IRRITANT CONTACT DERMATITIS

COMMITTEE IN CHARGE: *Randle M. Gallucci, PhD, Chair; Michael A. Ihnat, PhD, William Michael McShan, PhD; Robert D. Foreman, PhD; T. Kent Teague, PhD; David M. Sherry; PhD*

ABSTRACT: Irritant contact dermatitis (ICD), the most common form of occupational dermatitis, is an inflammatory response of the skin to chemical or physical agents. Following irritant exposure, keratinocytes release a myriad of cytokines including IL-6. Myeloid cells, which include macrophages and neutrophils, have been shown to infiltrate the skin during ICD. Our group has determined that IL-6 confers a protective effect to lesional skin during ICD. How IL-6Rα function in keratinocytes and myeloid cells influences the pathomechanism of ICD is unknown.

To investigate how IL-6Rα influences the inflammatory response during ICD, keratinocyte-specific IL-6Rα knockout mice ($Il6ra^{\Delta ker}$), myeloid-specific IL-6Rα knockout mice ($Il6ra^{\Delta myeloid}$), and littermate controls were exposed to benzalkonium chloride (BKC), Jet propellant 8 (JP-8) fuel, two well-characterized occupational irritants, or acetone control for 3 or 7 consecutive days. Lesional skin was collected from each mouse genotype and immune cell influx was characterized by histopathology,

immunohistochemistry and flow cytometry. Inflammatory cytokine protein expression was determined with multiplex immunoassay.

Our results show that deficiency of IL-6Rα in both cell types led to an exaggerated inflammatory response to the irritants used. Indeed, histopathology revealed higher immune cell infiltration and epidermal hyperplasia in both $Il6ra^{\Delta ker}$ and $Il6ra^{\Delta myeloid}$ mice relative to WT. Flow cytometry revealed $Il6ra^{\Delta ker}$ and $Il6ra^{\Delta myeloid}$ mouse skin had increased numbers of $CD11b^{+}CD45^{+}$ and $CD11b^{+}Ly6C^{+}$ cells respectively but reduced numbers $CD3^{+}$ γδ TCR^{+} (γδT) and $CD11b^{+}F4/80^{+}$ cells respectively relative to WT after irritant exposure. Furthermore, $IL\text{-}6R\alpha^{\Delta ker}$ and $Il6ra^{\Delta myeloid}$ mouse skin displayed higher levels of pro-inflammatory cytokine proteins including IL-1α, IL-1β, and TNF-α.

Interestingly, $Il6ra^{\Delta ker}$ mouse skin displayed higher levels of IL-22 and IL-22Rα proteins relative to WT after BKC exposure. It was also determined, through *in vitro* experiments, that IL-6 negatively regulates the expression of IL-22Rα on epidermal keratinocytes. The effects of IL-22 on keratinocyte function were diminished in the presence of IL-6.

These results indicate the protective role of IL-6Rα in keratinocytes and myeloid cells during ICD. Also, results presented herein highlight a previously unknown link between IL-6 and the IL-22/IL-22Rα system in the skin and suggest a possible association between IL-22 and the epidermal hyperplasia that occurs during ICD.