Controlling cell death prevents skin inflammation

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The outer layer of the skin, called the epidermis, forms a critical physical and immunological wall that serves as the body's first line of defense against potentially harmful microorganisms. Most of the epidermis consists of cells called keratinocytes that build a mechanical barrier but also perform immune functions. Now, a new study published by Cell Press in the October issue of the journal *Immunity* provides evidence that stopping of a type of regulated cell death called "necroptosis" in keratinocytes is critical for the prevention of skin inflammation.

The Fas Associated Death Domain (FADD) protein interacts with "death receptors" to activate a well-known programmed cell death pathway called apoptosis. Death receptors have also been shown to induce necroptosis, which is a different type of cell death and is mediated by the proteins RIP1 and RIP3. "Previous studies have suggested that prevention of RIP-mediated necroptosis is essential for embryonic development," says senior study author, Dr. Manolis Pasparakis, from the University of Cologne. "However, the physiological significance of the mechanisms regulating necroptosis for normal tissue function and disease pathogenesis remains unclear."

Dr. Pasparakis and colleagues discovered that mice with epidermis-specific ablation of FADD showed spontaneous necroptosis of keratinocytes and developed severe inflammatory skin lesions within a few days of birth. Further, RIP3-dependent necrotic death of FADD-deficient keratinocytes was identified as the initiating event triggering

skin inflammation. "In contrast to the well-established role as a mediator of apoptosis, we discovered that FADD performs an essential pro-survival function in keratinocytes that is crucial for the maintenance of a balanced skin immune response and the prevention of skin inflammation," reports Dr. Pasparakis.

Taken together, the findings reveal a previously unrecognized physiological role for FADD in preventing necroptosis of epidermal keratinocytes and identify sensitization of keratinocytes to RIP3-mediated cell death as a potent mechanism triggering skin inflammation. Further, these results suggest that genetic or external factors sensitizing keratinocytes necroptosis could be implicated in the pathogenesis of skin inflammation, a feature of many chronic or acute skin conditions such as eczema, psoriasis, and drug rashes. "Our findings provide a first experimental paradigm that regulation of necroptosis is important for the maintenance of immune homeostasis and the prevention of inflammation in the skin," concludes Dr Pasparakis.

Provided by Cell Press