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Research Scientist Prof. Manolis Pasparakis - Cologne: Protein regulating cell death prevents skin inflammation

Prof. Manolis Pasparakis and his colleagues at CECAD – the Cluster of Excellence for Aging Research – and Collaborative Research Centre 829 at the University of Cologne have made a breakthrough with their research into necroptosis – a form of programmed cell death.

The outer layer of the skin, called the epidermis, forms a critical physical and immunological barrier that serves as the body's first line of defence against potentially harmful microorganisms. Most of the epidermis consists of cells called keratinocytes, which build a mechanical barrier but also perform immune functions. A new study published in the October issue of the journal Immunity provides evidence that modulation 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, a different type of cell death that 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 CECAD, the Cluster of Excellence at 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 its 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.

Please address any queries to:
Prof. Manolis Pasparakis, phone +49 (0) 221-470-1526
pasparakis@uni-koeln.de

CECAD PR & Marketing
Astrid Bergmeister, phone + 49 (0) 221-470-5287
astrid.bergmeister@uk-koeln.de
Andrea Pfennig, phone + 49 (0) 221-470-1603
andrea.pfennig@uk-koeln.de