

## Intrinsic alterations in nonlesional epidermis spur the inflammatory process in vitiligo

Vitiligo involves inflammatory processes that direct an autoimmune response against melanocytes through a complex mechanism that may involve inherited functional defects of cells in pigmented skin. Kovacs et al. (2022) showed that nonlesional vitiligo keratinocytes (KCs) exhibited enlarged morphology, low proliferation rates, and impaired differentiation and stratification. Observations of low adenosine triphosphate levels in these KCs suggested that these cells may not produce sufficient energy to correctly differentiate and stratify. Furthermore, epidermal lipid composition in nonlesional KCs was altered, with decreased levels of ceramide and increased levels of free fatty acids, cholesterol (CHOL), and CHOL sulfate. Defects in KC differentiation and lipid composition may result in defects of the outer skin barrier. Together with the finding that vitiligo KCs secreted several inflammatory mediators, including CXCL10, IL-6, and IL-1 $\beta$ , the authors conclude that the intrinsic changes of nonlesional epidermis in vitiligo can serve as an important initiator stimulating the immune response against melanocytes. (*Sci Adv* 8:eabn9299, 2022; <https://doi.org/10.1126/sciadv.abn9299>) Selected by E. Tschachler

## Characterization of patients with monkeypox in Spain

Because the current outbreak of monkeypox has presented differently from infections in African countries where it is endemic, Tarin-Vicente et al. (2022) conducted a multicenter, prospective, observational cohort study to investigate the clinical presentation and virological assessment of 181 patients (175 men, 6 women) with confirmed monkeypox diagnosis at three sexual health clinics in Madrid, Spain. Most patients presented with a small number of lesions in genital, oral, and/or anal regions and had experienced prodromal symptoms before the rash appeared. The median incubation period was 7 days, suggesting that postexposure vaccination is unlikely to be effective. The most common complications were proctitis, tonsillitis, paraphimosis, and bacterial abscesses, but only 3 of the 181 patients required hospital admission. The viral load detected in lesional swabs was significantly higher than that in pharyngeal swabs. Together, these data confirm that close contact during sex is the primary transmission route for monkeypox infection, whereas respiratory transmission is very likely less relevant. (*Lancet* 400:661–9, 2022; [https://doi.org/10.1016/S0140-6736\(22\)01349-6](https://doi.org/10.1016/S0140-6736(22)01349-6)) Selected by E. Tschachler

## Jak inhibition improves cutaneous and pulmonary sarcoidosis

Although the pathogenesis of characteristic noncaseating granuloma in the inflammatory disorder sarcoidosis is not well-defined, many cytokines and chemokines have been implicated. Because many of these factors signal through the Jak/signal transducer and activator of transcription pathway, Damsky et al. (2022) recently conducted a prospective open-label trial of treatment with the Jak inhibitor tofacitinib in 10 patients with long-standing cutaneous sarcoidosis and previous stable immunomodulatory treatment. A subset of these patients also had internal organ involvement. Disease control after 6

months of tofacitinib treatment was superior to the preceding immunotherapy in all 10 patients, with six patients showing a complete response. The improvement was observed for skin disease as well as internal organ involvement. An increased dosage in two of the patients with partial response led to further disease improvement. Molecular studies revealed that IFN- $\gamma$ , which functions as an important driver of macrophage activation, and additional type 1 cytokines were associated with both disease activity and response to tofacitinib therapy. (*Nat Commun* 13:3140, 2022; <https://doi.org/10.1038/s41467-022-30615-x>) Selected by M. Wittmann

## Broad range of autoimmune diseases are associated with an increased risk of cardiovascular diseases

Chronic systemic inflammation is thought to underlie the reported association between some autoimmune diseases and increased cardiovascular risk. To expand the understanding of this relationship, Conrad et al. (2022) performed a large observational population-based study to assess the association between the 19 most common autoimmune diseases and a broad range of cardiovascular outcomes. In more than 440,000 cases and 2,100,000 matched controls, patients with autoimmune disorders had an increased risk of incident cardiovascular disease compared with those without autoimmune disorders. All the 19 examined autoimmune disorders were associated with increased risk, and systemic sclerosis, Addison disease, systemic lupus erythematosus, and type 1 diabetes had the highest cardiovascular risk. These autoimmune disorders were associated with a whole range of cardiovascular disorders, beyond atherosclerotic disease, which is known to be associated with autoimmunity. Increased cardiovascular risk was especially pronounced in younger patients and was not attributable to traditional cardiovascular risk factors in these patients. These findings may have implications for early targeted cardiovascular prevention measures in younger patients with autoimmune disease. (*Lancet* 400:733–43, 2022; [https://doi.org/10.1016/S0140-6736\(22\)01349-6](https://doi.org/10.1016/S0140-6736(22)01349-6)) Selected by J. Gelfand

## Anatomic miswiring of Merkel cells with pruriceptors in chronic itch

An incomplete understanding of the mechanisms underlying chronic itch plagues the development of effective treatments for this debilitating problem. Although mechanical stimuli, including scratching, can transiently suppress itch, persistent scratching can actually aggravate itch through the release of proinflammatory mediators. Feng et al. (2022) found that although Merkel cells drive slowly adapting type I fiber firing to suppress mechanical itch under physiological conditions, in chronic itch, they drive C fibers to evoke scratch-induced itch: mechanical stimulation of the skin leads to the activation of Piezo2 channels on Merkel cells and results in subsequent C-fiber firing to induce spontaneous scratching behavior in a setting of dry skin state. Observation of miswiring of skin-innervating MRGPRA3-expressing nerve fibers toward Merkel cells in the skin suggests a pathological touch receptor–pruritogenic circuit to promote scratch-induced itch in a murine model. These studies unveil a dynamic mechanism by which touch receptors trigger pruriceptor firing in the skin to stimulate the itch–scratch cycle and highlight potential interactions for future therapeutic exploration. (*Sci Transl Med* 14:eabn4819, 2022; <https://doi.org/10.1126/scitranslmed.abn4819>) Selected by M. Tomic-Canic