of cells within the skin are capable of giving rise to the tumors now collectively called MCC. These two important reports show that one path is through a keratinocytic intraepidermal precursor and suggest that keratinocytes can serve as a cell of origin for MCPyV-negative MCC.

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**CONFLICT OF INTEREST**

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**REFERENCES**


**See related article on pg 571**

New Key Players in Irritant Contact Dermatitis: Residential Skin Cells and Neutrophils Drive Inflammation

Antti Lauferma1, Paulina Werner2, Lukas Wisgrill3 and Nanna Fyhrquist2

The chemokine CCL2 is a potential biomarker for progression of inflammatory skin disease. In a new article of the Journal of Investigative Dermatology, Shibuya et al. (2021) use murine experimental models to show that CCL2–CCR2–dependent IL-1β secretion by local skin cells and skin-infiltrating neutrophils are key drivers of skin irritation.


Irritant contact dermatitis is a common disease that lacks effective treatment.

Irritant contact dermatitis (ICD) is a common inflammatory skin disease that is caused by irritants, including chemicals, direct friction, and wet work. It is commonly expressed as hand eczema, and as such, it is an increasingly important cause of work-related disease (Reinholz et al., 2021). The mechanism of ICD is not well-characterized, and this hampers both differentiation from allergic contact dermatitis and initiation of proper treatment. ICD can be treated with topical and systemic corticosteroids, but responses to other therapies such as calcineurin inhibitors and UV are less effective. In chronic cases, ICD can be treated with systemic retinoid analogs (Diepgen et al., 2015). However, new treatments for this debilitating disease are greatly needed (Bonnekoh et al., 2021).

CCR2–CCL2 signaling drives skin inflammation

In a new article of the Journal of Investigative Dermatology, Shibuya et al. (2021) identify novel cellular mechanisms that are crucial for the induction of skin irritation through a complementary series of murine knockout, chimeric, and parabiosis experiments. The authors hypothesized that the CCL2–CCR2 axis might be important in driving ICD-associated skin inflammation. CCL2 has previously been implicated as a key mediator of inflammation in various organs (Chen et al., 2020; Dimitrijevic et al., 2007; Wolf et al., 2019) as well as in inflammatory disorders, including atherosclerosis, rheumatoid arthritis, allergic

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asthma, psoriasis, and atopic dermatitis (AD) (Behfar et al., 2018; He et al., 2020; Jiang et al., 2019). Moreover, CCL2–CCR2 signaling appears to be involved in wound healing (Whelan et al., 2020). CCL2 exerts diverse functions on lymphoid and myeloid immune cells, showing immunomodulatory properties beyond chemotaxis (Gschwandtner et al., 2019). Interestingly, nonimmune cells such as endothelial cells, fibroblasts, and epithelial cells also produce CCL2. CCL2 secretion in the skin appears to recruit inflammatory monocytes, dendritic cells (DCs), and memory T cells. The receptors that bind CCL2 include CCR1, CCR2, and CCR3. CCR2 is the main receptor for CCL2 in inflammation, and it is highly expressed by blood monocytes and skin macrophages (Dyer et al., 2019).

To test the hypothesis that the CCL2–CCR2 axis might be involved in ICD, Shibuya et al. (2021) used both CCL2- and CCR2-deficient mice. Both strains showed attenuated cumulative ICD responses to repeated-dose exposure to the irritant SDS, exhibiting less ear swelling; transsepidermal water loss; and recruitment of neutrophils, monocytes, and eosinophils. These results suggested that the CCL2–CCR2 axis is a key driver of this type of inflammation.

To learn whether Ccr2−/− cells responsible for ICD are circulating cells, the authors constructed chimeras with bone marrow (BM) transplanted from wild-type (WT) or Ccr2−/− mice to either WT or Ccr2−/− mice that had their own BM removed by irradiation (Holl, 2013). When CCR2 was lacking in the radioresistant cell compartment, ICD responses were attenuated, and WT BM could not rescue the response. In contrast, when irradiated WT mice were reconstituted with Ccr2−/− BM, fully blown ICD responses developed, including ear swelling and infiltration of neutrophils and eosinophils. Strikingly, in Ccr2−/− BM-reconstituted WT mice, there was no visible infiltration of monocytes. These results showed that monocytes are redundant to CCR2-dependent induction of SDS-induced ICD.

The attenuated accumulation of circulating cells was not due to inadequate BM engraftment because circulating cells in peripheral blood were similar in both WT and Ccr2−/− chimeras. To gain further insights into the mechanism, the authors created para-bionts (see Supplementary Figure in the article) in which two mice, one Ccr2−/− (CD45.2+) and one WT (CD45.1+), were surgically joined to share a common blood circulation, as shown by the fact that half of the peripheral blood cells were CD45.1+, and half were CD45.2+. When the ears of the two parabiont mice were treated with SDS, the ICD response was attenuated in Ccr2−/− mice but not in the WT mice, shown by the measurement of ear swelling and the accumulation of monocytes and neutrophils. This proved that the CCR2-mediated effect, resulting in ICD, is dependent on cells that are resident in the skin and not on inflammatory cells that are recruited from blood.

IL-1β production is sufficient and necessary for the development of skin irritation

The inflammatory response in ICD results from activated innate immune signaling after skin damage caused by external stimuli (Lee et al., 2013). To assess the role of innate immune cells in ICD, Shibuya et al. (2021) treated mice with anti-Ly6G (Boivin et al., 2020) to remove neutrophils. This resulted in the amelioration of ICD and impairment not only of neutrophil infiltration but also of the recruitment of eosinophils and monocytes, suggesting that neutrophils are key players in CCR2-mediated ICD.

Finally, RNA-sequencing analysis revealed that Ccr2−/− mice have significantly lower expression of neutrophil migration-associated genes,
including II1β, than WT mice. IL-1β neutralization with antibody also attenuated neutrophil accumulation in WT mice, whereas intradermal injection of IL-1β restored ICD in both WT mice treated with IL-1β antibody and Ccr2-/- mice. This suggests that CCR2-dependent production of IL-1β is critical for the development of ICD.

What are the radiosensitive cells that this study pinpoints as responsible for IL-1β production and the initiation of ICD? Their exact location and identity are not yet established, but Shibuya et al. (2021) showed that the majority of IL-1β-expressing skin cells stain positive for vimentin. Vimentin was initially discovered in fibroblasts (Geisler et al., 1983) but has now been detected in various immature cells, including mesenchymal stem cells (MSCs). In human skin, vimentin is expressed in fibroblasts, endothelial cells, blood vessels, in smooth vascular musculature, in melanocytes, in macrophages, and in T cells (Uhlén et al., 2015).

MSCs migrate to sites of inflammation, and they have recently gained considerable attention in the context of skin inflammation. MSCs have a potent immunoregulatory capacity (Castro-Manrreza and Montesinos, 2015), and they promote wound healing in a CCL2-dependent manner (Whelan et al., 2020). MSCs can be isolated from both epidermal and dermal layers of the skin (Castro-Manrreza et al., 2019), and they have been observed in psoriasis (Liu et al., 2014), but whether they contribute to this disease remains to be established. A considerable obstacle in MSC-related investigations is the lack of definitive markers, requiring the utilization of a number of criteria to identify MSCs with certainty.

Shibuya et al. (2021) show that many of the CCL2-positive cells in SDS-irritated skin are positive for vimentin, suggesting the involvement of fibroblasts; endothelial cells; smooth muscle cells; or perhaps other skin resident cells, such as MSCs, as sources of this pivotal chemokine. An inflammatory role for fibroblasts has recently been proposed by He et al. (2020), who explored the skin transcriptome in AD at the single-cell level. Their study revealed a novel subset of fibroblasts expressing both CCL2 and CCL19 that interacted closely with DCs and macrophages. Previous studies have shown that binding of CCL2 to CCR2 triggers nuclear translocation of NF-KB, which is crucial for DC maturation and migration from the skin to draining lymph nodes for antigen presentation to T cells (Jimenez et al., 2010).

Nevertheless, the identity of the skin-resident, radiosensitive cell that responds to CCL2 and produces IL-1β remains a mystery. In the skin, the main cell types that express CCR2 are tissue-resident leukocytes. In contrast to most leukocytes, many of these tissue-resident leukocytes are highly radiosensitive, including macrophages and DCs with fetal origin (Bogunovic et al., 2006) or mast cells (Soule et al., 2007). Importantly, CCL2–CCR2 signaling activates both DC and macrophages, and it triggers mast cell degranulation (Campbell et al., 1999). Thus, it is possible that the responsible cell type is a tissue-resident macrophage, an Langerhans cell, or a mast cell or a combination thereof (Figure 1).

Conclusion and remaining questions

In aggregate, the results of Shibuya et al. (2021) and others suggest a key role for skin-resident cells in driving skin irritation, involving intrinsic cell to cell communication involving the CCL2–CCR2 axis. The study by Shibuya et al. (2021) uniquely pinpoints the local production of IL-1β and the recruitment of neutrophils as key initiators of skin irritation. Surprisingly, the study shows that monocytes play a minor role in the context, although many other studies have identified this cell subset as a major player in conditions such as psoriasis (Behfar et al., 2018) or wound healing (Whelan et al., 2020). The exact role and nature of the mechanisms that lead to IL-1β production and the cellular source of IL-1β remain unknown. In future studies, it will be important to determine whether this phenomenon is generalizable to all types of irritant reactions irrespective of the causative agent and importantly to human ICD.

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REFERENCES

Exhausted Markers in Cutaneous T-Cell Lymphoma: The Face that Launched a Thousand Ships

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Immune-modulatory therapies are widely appreciated to rejuvenate host antitumor immunity and improve mortality in solid-organ cancers. Targeting the exhausted markers such as PD-1, CTLA4, TIM3, LAG3 are particularly attractive owing to the activation of the immune response. However, their role in cutaneous T-cell lymphomas is less defined owing to the expression of those exhausted markers on both nonmalignant and malignant lymphocytes. In a new article of the Journal of Investigative Dermatology, Han et al. (2021) showed that microRNAs in malignant T cells could regulate the expression of PD-1, CTLA4, TIM3, and LAG3 and simultaneously mediate evasion from immune surveillance. These findings get us one step closer in our further investigation of whether those molecules could be targeted therapeutically.


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