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DIRA, DITRA, and New Insights Into Pathways of Skin Inflammation:

What's in a Name?

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Dermatology has a long-standing affinity for acronyms. From AGE¹ (acute generalized exanthematous pustulosis) to XP (xeroderma pigmentosum), acronyms have become a part of our dermatology lexicon, perhaps occasionally to the consternation of our colleagues in other specialties. In this issue, Brau-Javier et al¹ describe a patient with a severe pustular skin disease called “DIRA”—an acronym for “deficiency of the interleukin 1 (IL-1) receptor antagonist,” which we first described in 9 pediatric patients in 2009.² As its name suggests, DIRA is a new autoinflammatory disease linked to activation of the IL-1 pathway (Figure), joining the ranks of other IL-1–associated conditions with a prominent dermatologic component, foremost the cryopyrin-associated periodic fever syndromes (CAPS)—familial cold-induced autoinflammatory syndrome (FCAS), Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disease (NOMID).³

CAPS is caused by gain of function mutations that lead to oversecretion of the well-established fever causing cytokine IL-1 β , and all 3 disorders manifest in the skin as neutrophilic urticaria. In contrast, DIRA presents in the neonatal period with a severe neutrophilic “pustular” skin eruption, skin pathergy, and nail dystrophy, as well as elevated acute-phase reactants, sterile osteomyelitis, and periostitis. DIRA is caused by loss of function of the IL-1 receptor (IL-1R) antagonist, the first endogenous cytokine receptor antagonist identified that blocks IL-1 signaling (Figure). Absence of the IL-1R antagonist results in unopposed proinflammatory signaling via the cytokines IL-1 α and IL-1 β on the IL-1R type I (IL-1RI).

DIRA is a rare condition that you may never encounter in your practice, so why bother filing away another acronym in the deep recesses of your dermatologic cortex? First, as Brau-Javier et al¹ demonstrate, just as with CAPS, DIRA is exquisitely responsive to IL-1 blockade. Responses are similar to those seen following anti-IL-1 treatment for NOMID, the most severe form of CAPS; children who have been ill since infancy now feel well for the first time; others confined to wheelchairs because of disabling joint pain are able to walk; and growth curves begin to arc upward again for the first time in years. Interleukin 1–blocking therapy is now the standard of care for CAPS, and 3 Food and Drug Administration–approved agents, anakinra, rilonacept, and canakinumab, are currently available that provide targeted inhibition of IL-1 signaling.⁴

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Second, understanding DIRA may yield new insights into the mechanism of other challenging pustular skin conditions. The cutaneous and systemic features of DIRA bear similarity to features seen in pustular psoriasis and SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, and osteitis), suggesting that IL-1 signaling may play a role in these conditions as well.

DITRA, A NOVEL MONOGENIC FORM OF PUSTULAR PSORIASIS

The scientific rationale to explore the IL-1 family in skin inflammation has recently been bolstered by 2 studies that identified mutations in the gene encoding the IL-36 receptor (IL-36R) antagonist, *IL-36RN*, in familial⁵ and sporadic⁶ cases of generalized pustular psoriasis. This condition has been termed *DITRA*, an acronym for deficiency of the IL-36R antagonist (IL-36Ra). Interleukin 36Ra is an IL-1 family member that antagonizes the proinflammatory signals of IL-36 α , IL-36 β , and IL-36 γ at the IL-36R in a manner analogous to the effect of IL-1Ra inhibition on IL-1 responses (Table and Figure).^{7,8}

THE PUERTO RICAN DIRA FOUNDER DELETION

IL-36RN and the genes encoding the IL-36 agonist isoforms (*IL36A*, *IL36B*, and *IL36G*) sit in close proximity to *IL-1RN* on chromosome 2. In contrast to patients with DIRA from Newfoundland, Holland, Lebanon, and Brazil, who harbor isolated founder mutations in *IL-1RN*,^{2,9} patients with DIRA of Puerto Rican descent harbor a genomic deletion on chromosome 2, which encompasses *IL-1RN* as well as 5 adjacent genes: *IL36RN* (*IL1F5*), *IL36A* (*IL1F6*), *IL36B* (*IL1F8*), *IL36G* (*IL1F9*), and *IL38* (*IL1F10*). The estimated allele frequency of this founder deletion in the harbor area of Arecibo in the northern part of Puerto Rico is 1.3%.^{2,10}

Deletion of *IL36RN* in addition to *IL-1RN* raises the question of whether IL-36 signaling plays an independent role in the development of skin pustulosis in the Puerto Rican patients with DIRA. Interestingly, treatment with anakinra in 2 patients with the Puerto Rican founder mutation, including the Puerto Rican patient described by Brau-Javier et al,¹ did not lead to complete normalization of inflammatory markers. However, another reported patient homozygous for the Puerto Rican mutation who initiated anti-IL-1 therapy at a much younger age¹⁰ and our subsequent experience in 2 other Puerto Rican children who began treatment at a young age, confirms that complete response to anti-IL-1 therapy is achievable in the Puerto Rican patients with DIRA. Furthermore, the genomic deletion in Puerto Rican patients with DIRA also encompasses the 3 IL-36R agonists (IL-36 α , IL-36 β , and IL-36 γ) and likely cancels out the deleterious effect of loss of IL-36Ra (Figure). The ramifications of the loss of IL-38 in Puerto Rican patients with DIRA is unclear because little is known about the function of the cytokine or its receptor; however, severe bony overgrowth such as that described by Brau-Javier et al¹ has only been described in Puerto Rican patients with DIRA, raising the possibility of a role for the cytokine in the development of the osseous deformities.

DIRA, DITRA, AND BEYOND

Interleukin 1R1 and IL-1Ra are ubiquitously expressed,¹¹ whereas expression of IL-36R is restricted to epithelial cells in direct contact with the environment, including the skin,^{12,13} which may explain the lack of bone involvement in DITRA in contrast to DIRA. However, the clinical and histological similarities of skin involvement raise the possibility of a common downstream pathway to pustular skin inflammation.

Several years prior to the discovery of DITRA, the role of IL-36 in skin inflammation was examined in a murine model that overexpressed IL-36 α (*il1f6*) in the epidermis under a keratin promoter.¹⁴ The transgenic mice developed pustular skin lesions, and when bred

onto a genetic background that lacks the IL-36Ra (*il1f5*), the disease worsened, independent of T-cell involvement. An increase in IL-36 α expression in psoriasis vulgaris also suggests that the IL-36 isoforms may play a pivotal role in pustular and plaque-type psoriasis.¹⁵ The IL-36 isoforms are potent inducers of a proinflammatory cytokine network that is also up-regulated in psoriatic skin disease and can initiate the recruitment of inflammatory cells into the skin, including neutrophils, T-cells, and myeloid dendritic cells, thereby fueling and perpetuating the inflammatory response.^{15–17} Interestingly, when the *IL36 α /IL1F6* transgenic mice were crossed onto an *IL1R1*-deficient background, disease severity was not attenuated, suggesting the IL-1R is not required to mediate the IL-36 model pustular phenotype.¹⁴ These results would predict that in contrast to DIRA, patients with DITRA may not respond to IL-1 blockade; however, clinical confirmation is needed.

Both IL-1Ra¹⁸ and IL-36Ra¹⁹ are highly expressed in keratinocytes. It is conceivable that the IL-36 isoforms may modulate skin pustulosis downstream of IL-1 in DIRA as well as other genetically undefined pustular skin diseases. However, the Puerto Rican patients with DIRA manifest prominent skin pustulosis despite the absence of all the IL-36 isoforms, suggesting that IL-1 and IL-36 may act independently in skin inflammation.

Can the knowledge we have gained by understanding 2 rare monogenic diseases, DIRA and DITRA, be generalized to other neutrophilic disorders? In a second Cutting Edge article in this issue, Lutz and Lipsker²⁰ test the hypothesis that IL-1 blockade may have utility in pustular psoriatic disease in a patient with no genetically characterized abnormality. The authors describe a 59-year-old woman with acrodermatitis of Hallopeau and recurrent fevers unresponsive to multiple therapies, including psoralen UV-A, acitretin, methotrexate, and 3 tumor necrosis factor inhibitors. Treatment with anakinra, initially in combination with acitretin and subsequently as monotherapy, led to resolution of pustules within 24 hours and normalization of C-reactive protein within 5 days.²⁰ Similar results were recently reported in 2 patients with generalized pustular psoriasis following anakinra treatment.²¹ In this earlier report, elevated serum IL-6 (283 ng/L; reference range, 0–8.6 ng/L) and IL-1B (22.4 ng/L; reference range, 0–15 ng/L) levels in one of the patients returned to normal during therapy.

Anecdotal reports have also described efficacy of anti-IL-1 therapy in Sweet syndrome,²² neutrophilic urticarial dermatosis,²³ and neutrophilic panniculitis.²⁴ However, this approach is unlikely to be a panacea for all neutrophilic skin disease, including one of the most common, plaque-type psoriasis. Despite rapid improvement in skin pustule formation and systemic inflammation, the patient described by Lutz and Lipsker²⁰ did not have improvement in the papulosquamous component of her skin disease. Similarly, in a study of anakinra for psoriatic arthritis, only 2 of 8 patients with significant skin involvement had improvement. In addition, skin disease worsened in 4 of 8, and 1 patient developed new-onset psoriasis during anakinra treatment.²⁵

The monogenic diseases DIRA and DITRA, albeit rare, are important “experiments in nature” that enhance our understanding of pathways leading to skin inflammation. Dramatic responses to IL-1 blockade in DIRA provide a tantalizing opportunity to consider other dermatologic applications, particularly challenging neutrophilic disorders. If IL-1 and IL-36 independently contribute to skin inflammation, one might expect that patients with pustular skin inflammation triggered primarily by IL-1 will respond to IL-1 blockade. Others may require treatment targeting IL-36 directly or common downstream pathways. Regardless, understanding these rare monogenic diseases brings us one step closer to moving from acronyms to answers for patients with severe skin disease.

REFERENCES

1. Brau-Javier CN, Gonzales-Chavez J, Toro JR. Chronic cutaneous pustulosis due to a 175-kb deletion on chromosome 2q13: excellent response to anakinra. *Arch Dermatol.* 2012; 148(3):301–304. [PubMed: 22431772]
2. Aksentijevich I, Masters SL, Ferguson PJ, et al. An autoinflammatory disease with deficiency of the interleukin-1-receptor antagonist. *N Engl J Med.* 2009; 360(23):2426–2437. [PubMed: 19494218]
3. Goldbach-Mansky R, Kastner DL. Autoinflammation: the prominent role of IL-1 in monogenic autoinflammatory diseases and implications for common illnesses. *J Allergy Clin Immunol.* 2009; 124(6):1141–1149. [PubMed: 20004775]
4. Goldbach-Mansky R. Current status of understanding the pathogenesis and management of patients with NOMID/CINCA. *Curr Rheumatol Rep.* 2011; 13(2):123–131. [PubMed: 21538043]
5. Marrakchi S, Guigue P, Renshaw BR, et al. Interleukin-36-receptor antagonist deficiency and generalized pustular psoriasis. *N Engl J Med.* 2011; 365(7):620–628. [PubMed: 21848462]
6. Onoufriadis A, Simpson MA, Pink AE, et al. Mutations in IL36RN/IL1F5 are associated with the severe episodic inflammatory skin disease known as generalized pustular psoriasis. *Am J Hum Genet.* 2011; 89(3):432–437. [PubMed: 21839423]
7. Debets R, Timans JC, Homey B, et al. Two novel IL-1 family members, IL-1 delta and IL-1 epsilon, function as an antagonist and agonist of NF-kappa B activation through the orphan IL-1 receptor-related protein 2. *J Immunol.* 2001; 167(3):1440–1446. [PubMed: 11466363]
8. Towne JE, Garka KE, Renshaw BR, Virca GD, Sims JE. Interleukin (IL)-1F6, IL-1F8, and IL-1F9 signal through IL-1Rrp2 and IL-1RAcP to activate the pathway leading to NF-kappaB and MAPKs. *J Biol Chem.* 2004; 279(14):13677–13688. [PubMed: 14734551]
9. Jesus AA, Osman M, Silva CA, et al. A novel mutation of IL1RN in the deficiency of interleukin-1 receptor antagonist syndrome: description of two unrelated cases from Brazil. *Arthritis Rheum.* 2011; 63(12):4007–4017. [PubMed: 22127713]
10. Reddy S, Jia S, Geoffrey R, et al. An autoinflammatory disease due to homozygous deletion of the IL1RN locus. *N Engl J Med.* 2009; 360(23):2438–2444. [PubMed: 19494219]
11. Dinarello CA. Biologic basis for interleukin-1 in disease. *Blood.* 1996; 87(6):2095–2147. [PubMed: 8630372]
12. Kumar S, McDonnell PC, Lehr R, et al. Identification and initial characterization of four novel members of the interleukin-1 family. *J Biol Chem.* 2000; 275(14):10308–10314. [PubMed: 10744718]
13. Smith DE, Renshaw BR, Ketchum RR, Kubin M, Garka KE, Sims JE. Four new members expand the interleukin-1 superfamily. *J Biol Chem.* 2000; 275(2):1169–1175. [PubMed: 10625660]
14. Blumberg H, Dinh H, Trueblood ES, et al. Opposing activities of two novel members of the IL-1 ligand family regulate skin inflammation. *J Exp Med.* 2007; 204(11):2603–2614. [PubMed: 17908936]
15. Blumberg H, Dinh H, Dean C Jr, et al. IL-1RL2 and its ligands contribute to the cytokine network in psoriasis. *J Immunol.* 2010; 185(7):4354–4362. [PubMed: 20833839]
16. Zaba LC, Fuentes-Duculan J, Eungdamrong NJ, et al. Psoriasis is characterized by accumulation of immunostimulatory and Th1/Th17 cell-polarizing myeloid dendritic cells. *J Invest Dermatol.* 2009; 129(1):79–88. [PubMed: 18633443]
17. Nestle FO, Di Meglio P, Qin JZ, Nickoloff BJ. Skin immune sentinels in health and disease. *Nat Rev Immunol.* 2009; 9(10):679–691. [PubMed: 19763149]
18. Bigler CF, Norris DA, Weston WL, Arend WP. Interleukin-1 receptor antagonist production by human keratinocytes. *J Invest Dermatol.* 1992; 98(1):38–44. [PubMed: 1530822]
19. Johnston A, Xing X, Guzman AM, et al. IL-1F5, -F6, -F8, and -F9: a novel IL-1 family signaling system that is active in psoriasis and promotes keratinocyte antimicrobial peptide expression. *J Immunol.* 2011; 186(4):2613–2622. [PubMed: 21242515]
20. Lutz V, Lipsker D. Acitretin- and tumor necrosis factor inhibitor-resistant acrodermatitis continua of Hallopeau responsive to the interleukin 1 receptor antagonist anakinra. *Arch Dermatol.* 2012; 148(3):297–299. [PubMed: 22431771]

21. Viguier M, Guigue P, Pagès C, Smahi A, Bachelez H. Successful treatment of generalized pustular psoriasis with the interleukin-1-receptor antagonist Anakinra: lack of correlation with IL1RN mutations. *Ann Intern Med.* 2010; 153(1):66–67. [PubMed: 20621920]
22. Kluger N, Gil-Bistes D, Guillot B, Bessis D. Efficacy of anti-interleukin-1 receptor antagonist anakinra (Kineret) in a case of refractory Sweet's syndrome. *Dermatology.* 2011; 222(2):123–127. [PubMed: 21464561]
23. Kieffer C, Cribier B, Lipsker D. Neutrophilic urticarial dermatosis: a variant of neutrophilic urticaria strongly associated with systemic disease: report of 9 new cases and review of the literature. *Medicine (Baltimore).* 2009; 88(1):23–31. [PubMed: 19352297]
24. Lipsker D, Perrigouard C, Foubert A, Cribier B. Anakinra for difficult-to-treat neutrophilic panniculitis: IL-1 blockade as a promising treatment option for neutrophil-mediated inflammatory skin disease. *Dermatology.* 2010; 220(3):264–267. [PubMed: 20197651]
25. Jung N, Hellmann M, Hoheisel R, et al. An open-label pilot study of the efficacy and safety of anakinra in patients with psoriatic arthritis refractory to or intolerant of methotrexate (MTX). *Clin Rheumatol.* 2010; 29(10):1169–1173. [PubMed: 20532937]

Figure.

The pathogenesis of DIRA (deficiency of the interleukin 1 [IL-1] receptor [IL-1R] antagonist) and DITRA (deficiency of the IL-36 receptor [IL-36R] antagonist). Loss of the IL-1R antagonist leads to unopposed proinflammatory signaling by IL-1 α and IL-1 β in patients with DIRA. In DITRA, loss of the IL-36R antagonist results in analogous unchecked signaling by IL-36 α , IL-36 β , and IL-36 γ at the IL-36R (right panel). Patients with DIRA from Puerto Rico harbor a genomic deletion in both the IL-1R antagonist (left panel) and IL-36R antagonist (center panel). Because the IL-36 proinflammatory signaling isoforms are also deleted, a functional consequence of loss of the IL-36R antagonist in Puerto Rican patients with DIRA is unlikely.

Table**Members of the Interleukin 1 (IL-1) Family**

Cytokine Name	IL-1 Family Member Name	Gene	Receptor/Coreceptor	Function
IL-1 α	IL-1F1	<i>IL1A</i>	IL-1R1/IL-1RAcP	Proinflammatory
IL-1 β	IL-1F2	<i>IL1B</i>	IL-1R1/IL-1RAcP	Proinflammatory
IL-1Ra	IL-1F3	<i>IL1RN</i>	IL-1R1	Antagonist of IL-1 α , IL-1 β
IL-18	IL-1F4	<i>IL18</i>	IL-18R α /IL-18R β	Proinflammatory
IL-36 α	IL-1F6	<i>IL36A</i>	IL-1Rrp2/IL-1RAcP	Proinflammatory
IL-36 β	IL-1F8	<i>IL36B</i>	IL-1Rrp2/IL-1RAcP	Proinflammatory
IL-36 γ	IL-1F9	<i>IL36G</i>	IL-1Rrp2/IL-1RAcP	Proinflammatory
IL-36Ra	IL-1F5	<i>IL36RN</i>	IL-1Rrp2	Antagonist of IL-36 α , IL-36 β , IL-36 γ
IL-33	IL-1F11	<i>IL33</i>	IL-1RL1/IL-1RAcP	T _H 2 responses, proinflammatory
IL-37	IL-1F7	<i>IL37</i>	IL-18R α /unknown	Anti-inflammatory
IL-38	IL-1F10	<i>IL38</i>	Unknown/unknown	Unknown

Abbreviations: IL, interleukin; IL-1R1, interleukin 1 receptor type I; IL-1Ra, interleukin 1 receptor antagonist; IL-1RAcP, interleukin 1 receptor accessory protein; IL-1RL1, interleukin 1 receptorlike 1; IL-1Rrp2, interleukin 1 receptor-related protein 2; IL-18R α , interleukin 18 receptor α ; IL-18R β , interleukin 18 receptor β ; IL-36Ra, interleukin 36 receptor antagonist; T_H2, helper T cell type 2.