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Monocytes from patients with atopic dermatitis are primed for superoxide production

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To determine the potential role of monocytes (peripheral blood monocytes, PBMs) in the pathogenesis of atopic dermatitis (AD), we investigated whether PBMs from patients with severe AD are primed to generate toxic oxygen metabolites. To induce in vitro superoxide anion (O_2^-) production, we used either particulate (e.g., opsonized bacteria or zymosan) or soluble (e.g., phorbol esters) stimuli, which allowed us to test two distinct pathways for reduced nicotinamide-adenine dinucleotide phosphate activation. In addition, PBMs from the same patients were also examined for their levels of expression of the low-affinity receptor for IgE, *Fc_ε* receptor 2 (CD23). We found that PBMs, but not peripheral blood neutrophils, from patients with AD were primed for O_2^- production as compared to PBMs from either normal control subjects or patients with allergic rhinitis. These cells also expressed increased levels of CD23, and there was a significant correlation between these two parameters. Since the monocytes infiltrating into the AD lesions bear CD23, our data suggest that in vivo priming of PBMs and increased O_2^- production may participate in the pathogenesis of this skin disease. (*J ALLERGY CLIN IMMUNOL* 1992;89:545-51.)

Key words: Atopic dermatitis, superoxide, monocytes

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AD is a chronic inflammatory skin disorder associated with elevated serum IgE levels.^{1, 2} The pathogenesis of AD is poorly understood. Although allergen-induced IgE-mediated type I reactions may contribute to the exacerbation of AD in some patients, such reactions probably do not account for all the clinical manifestations of this disease. Indeed, the skin lesion of chronic AD is characterized predominantly by infiltrating monocytes-macrophages bearing the low-affinity IgE receptor on their cell surface.^{3, 4}

Generation of toxic oxygen metabolites by activated leukocytes has been demonstrated to participate in tissue injury in a variety of inflammatory conditions.⁵ Mechanisms of tissue injury by oxygen-free radicals include lipid peroxidation of membranes, alterations in structural proteins or enzymes, and DNA damage, as well as chemotaxis and activation of inflammatory cells.^{6, 7} O_2^- is generated by phagocytic cells (monocytes, macrophages, and neutrophils) after activation of the respiratory-burst enzyme NADPH oxidase.⁸ Calhoun and Bush⁹ have recently reported evidence for increased oxidative metabolism by airspace cells recovered from the bronchoalveolar lavage fluid of subjects with asthma.

Taken together, these observations suggest that monocytes may participate in tissue injury and amplify inflammation by producing reactive oxygen species. We therefore undertook the present study to examine whether PBMs from patients with AD were primed to produce O_2^- and furthermore, whether this form of monocyte activation correlated with the expression of CD23 on their cell surface.

MATERIAL AND METHODS

Patients

We investigated nine patients with severe AD (as defined by clinical involvement of >50% of the skin surface and high IgE levels) diagnosed according to the criteria of Hanifin and Rajka.¹⁰ The patients with severe AD consisted of five male and four female patients. Their median age was 26 years (range, 12 to 36 years). Their median serum IgE level was 6120 IU/ml (range, 690 to 39,600 IU/ml). Their laboratory studies were compared to studies of nine normal nonatopic control subjects (five male and four female subjects with a median age of 27 years, ranging from 22 years to 38 years of age) and five patients with AR with ragweed sensitivity. The five patients with AR, three male and two female patients, were studied in June and July 1988, with a median age of 25 years (ranging from 22 to 29 years).

Cell preparations

Forty to sixty milliliters of blood was drawn in a heparinized syringe and diluted 1:1 (vol/vol) with Hanks' balanced salt solution (Gibco Laboratories, Grand Island, N.Y. or Paisley, Scotland). Peripheral blood mononuclear cells were isolated by Ficoll-Hypaque centrifugation, as previ-

Abbreviations used

AD:	Atopic dermatitis
O_2^- :	Superoxide anion
AR:	Allergic rhinitis
PBM:	Peripheral blood monocyte
SOD:	Superoxide dismutase
MAB:	Monoclonal antibody
PMA:	Phorbol myristate acetate
OZ:	Opsonized zymosan
NADPH:	Reduced nicotinamide-adenine dinucleotide phosphate
IL:	Interleukin

ously described.¹¹ Peripheral blood mononuclear cells were resuspended in culture medium and allowed to adhere to plastic tissue-culture flasks (Falcon, Becton Dickinson Labware, Lincoln Park, N.J.) for 45 minutes at 37° C. Non-adherent lymphocytes were decanted, and the plates were washed three times with room temperature phosphate-buffered saline. Ice-cold phosphate-buffered saline was then added to the adherent cells, and the plates were kept on ice for 5 minutes. The adherent monocytes were then removed from the plastic dishes by vigorous pipetting and, when this was necessary, by gentle scraping. No proteolytic enzymes or divalent cation chelators were used. The monocyte preparation was >96% pure as assessed by May-Grünwald-Giemsa and nonspecific esterase stainings. There was no differences in the proportion of nonadherent cells among the three groups of subjects studied. Cell viability of this adherent cell population was determined after the disadherence procedure and were >90% viable, as determined by trypan blue exclusion. The same disadhered monocyte cell preparations were studied for CD23 expression and superoxide generation. Neutrophils were isolated by dextran sedimentation and Ficoll-Hypaque gradient, as previously described.¹²

Measurement of superoxide production

Generation of O_2^- by PBMs was measured by the SOD-inhibitable reduction of ferricytochrome c, as previously described.¹³ PMA, zymosan, SOD, and cytochrome c were obtained from Sigma Chemical Co. (St. Louis, Mo.). Zymosan was opsonized with human serum, as previously described.¹⁴ In all experiments, PMA was used at 100 ng/ml and OZ at 3 mg/ml. Cells were stimulated for 30 minutes, since previous continuous recordings of cytochrome c reduction indicated a plateau at 30 minutes.¹³ In one patient with AD, one with AR, and three control subjects, measurement of O_2^- production by PBMs was done twice at 10- to 15-day intervals; in these cases, the value was recorded as the mean of the two experiments. In all cases, the numbers reported for O_2^- production are the mean of at least triplicate measurements unless it is otherwise indicated; values for SOD controls were subtracted for each corresponding condition. O_2^- production was expressed as nanomoles of O_2^- produced per 10^6 cells per 30 minutes.

Basal (unstimulated) O_2^- production was negligible under all conditions tested.

Immunofluorescence

The percentage of PBMs bearing Fc γ R2 (CD23) was assessed by indirect immunofluorescence. Briefly, 0.5×10^6 monocytes in staining buffer (RPMI 1640/2.5% fetal calf serum containing 0.01% sodium azide) were incubated for 30 minutes at 4° C with 1 μ g/ml of MAb 135 (CD23-specific MAb, generous gift of Dr. Guy Delespesse, Montreal). Cells were then washed and incubated with fluorescein isothiocyanate-conjugated goat antimouse immunoglobulin (Tago, Inc., Burlingame, Calif.) for 30 minutes at 4° C. As a control, an unrelated mouse IgG MAb was used, followed by fluorescein isothiocyanate-conjugated goat antimouse immunoglobulin under the same conditions. Forward angle and 90 degree light-scatter patterns were used to electronically gate on the monocyte populations that were easily distinguished from the contaminating small lymphocytes by flow cytometry. The percentage of cells reactive with MAb 135 was evaluated by a fluorescence-activated cell analyzer (Becton Dickinson). Background staining (always <5%) was subtracted from the experimental values.

Statistics

One-way analysis of variance with Scheffé F test was used to analyze significance between groups with respect to both O_2^- production and CD23 expression. Linear regression was used to establish correlations between O_2^- production after stimulation with either PMA or OZ, and PMA-stimulated O_2^- production with CD23 expression.

RESULTS

We found that basal (unstimulated) production of O_2^- by PBMs from patients with severe AD (mean $\pm$ SD, 1.1 ± 0.8) was not different from that of normal control subjects (mean $\pm$ SD, 0.6 ± 0.4 ; $p = 0.3$) or patients with AR (mean $\pm$ SD, 1.0 ± 1.0 ; $p = 0.8$). In contrast, O_2^- production triggered with either PMA (Fig. 1, A) or OZ (Fig. 1, B) was significantly higher in patients with severe AD than in normal control subjects or in patients with AR ($p < 0.0001$ and $p = 0.0002$, respectively, for PMA and OZ). In the patients with AD and AR (AD and AR taken together), there was a significant correlation between O_2^- production in response to these two distinct stimuli (Fig. 2; $r^2 = 0.759$), whereas this correlation was not significant in the control group ($r^2 = 0.075$, not presented). We also studied two patients with only approximately 10% skin involvement. Superoxide production by monocytes from these patients was 19.9 and 18.5 after stimulation with PMA, and 9.5 and 10.6 after stimulation with OZ. These values were within the normal range and therefore suggest that superoxide production is not elevated in monocytes from patients with mild AD. We also stud-

ied neutrophils from six patients with AD and six nonatopic control subjects for PMA-triggered O_2^- production. We found no increase in O_2^- production by PMA-stimulated peripheral blood neutrophils from patients with AD (Fig. 3).

CD23 expression of PBMs from normal control subjects was negligible (mean $\pm$ SD, $1\% \pm 1\%$). Patients with AR did not have significantly elevated CD23 expression, $6\% \pm 6\%$. In contrast, as illustrated in Fig. 4, CD23 expression on PBMs from patients with severe AD was significantly higher ($19\% \pm 9\%$) than in normal control subjects and in patients with AR. Although there was no statistically significant difference between control subjects and patients with AR for O_2^- production, two of these patients (patients with higher levels of expression of CD23, 10% and 15%, respectively) also had higher levels of PMA-stimulated O_2^- production (23.8 and 23.4 nmol of O_2^- per 10^6 cells per 30 minutes, respectively). Furthermore, we also found a significant correlation between PMA-stimulated O_2^- production and CD23 expression ($r = 0.446$; $p = 0.01$) (Fig. 5).

DISCUSSION

To determine the role of PBMs in the pathogenesis of AD, we investigated whether PBMs from patients with severe AD are primed to generate toxic oxygen metabolites, in particular, O_2^- . We examined two distinct pathways for NADPH activation¹⁵: generation of O_2^- by particulate (e.g., opsonized bacteria or OZ) versus soluble (e.g., phorbol esters) stimuli. In addition, PBMs from the same patients were simultaneously examined for their levels of surface expression of the low-affinity receptor for IgE (CD23). Our present findings indicate that PBMs of patients with severe AD are primed to release toxic oxygen products. Furthermore, these cells also express increased levels of CD23.

We found that both pathways for NADPH oxidase activation tested (direct activation of protein kinase C by PMA or phospholipase A₂-dependent metabolism of arachidonic acid) were primed. This finding suggests that the respiratory enzyme NADPH oxidase itself was primed rather than a specific second messenger. Interestingly, the correlation between O_2^- production stimulated either by PMA or by OZ was even better for patients (AR and AD) than for control subjects, further supporting the hypothesis of a general activation of the respiratory-burst enzyme associated with the disease process. In this study, PBMs from patients with AR were used as a control for mild allergic disease. Since the localized inflammation in AR may not be reflected in the circulation, no infer-

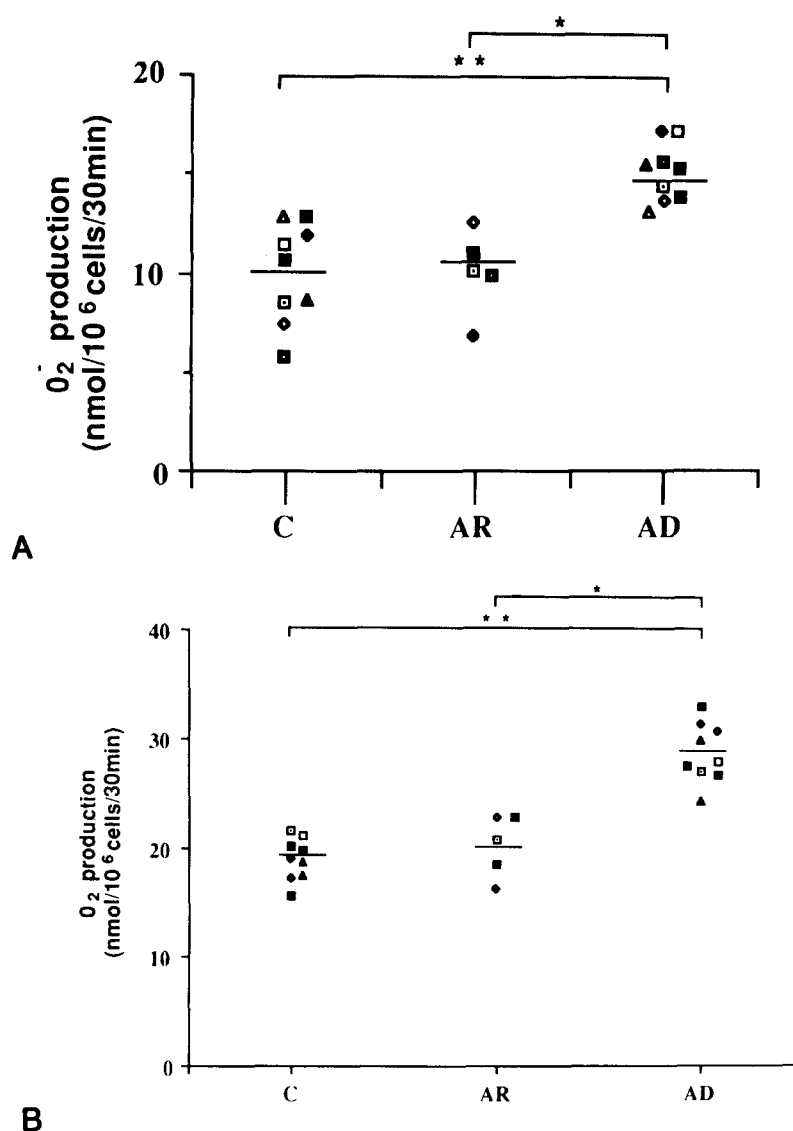


FIG. 1. A, Comparison of superoxide production after stimulation with PMA by PBMs from patients with AR and AD and control subjects (C). O_2^- production was significantly higher in patients with AD than in control subjects (**Scheffé F test, 27.63; $p < 0.001$) or in patients with AR (*Scheffé F test, 14.83; $p < 0.001$); no difference between control subjects and patients with AR. **B,** Comparison of superoxide production after stimulation with OZ by PBMs from patients with AR and AD and control subjects (C). O_2^- production was significantly higher in patients with AD than in control subjects (**Scheffé F test, 11.1; $p = 0.002$) or in patients with AR (*Scheffé F test, 8.29; $p = 0.002$); no difference between control subjects and patients with AR.

ences can be drawn from the different levels of superoxide production found in PBMs from patients with AD and AR.

In contrast to AD, the enhanced reactive oxygen metabolism also found in asthma after antigen challenge was significant only after *in vitro* activation of airspace cells by PMAs but not by OZ.⁹ In patients with asthma, the enhanced superoxide production may originate from granulocytes rather than monocytes, which could explain, at least in part, these differ-

ences.¹⁶ In our study, superoxide release triggered by PMA was maximal in granulocytes isolated from patients with AD and normal control subjects. Hence, there was no significant difference between the two groups. The enhanced oxidative capacity of monocytes appears to be a feature of AD and probably contributes to the pathogenesis of this disease.

Several potential mechanisms may result in the activation of monocytes in AD. First, cells of monocytic lineage bear the low-affinity receptor for IgE (CD23)

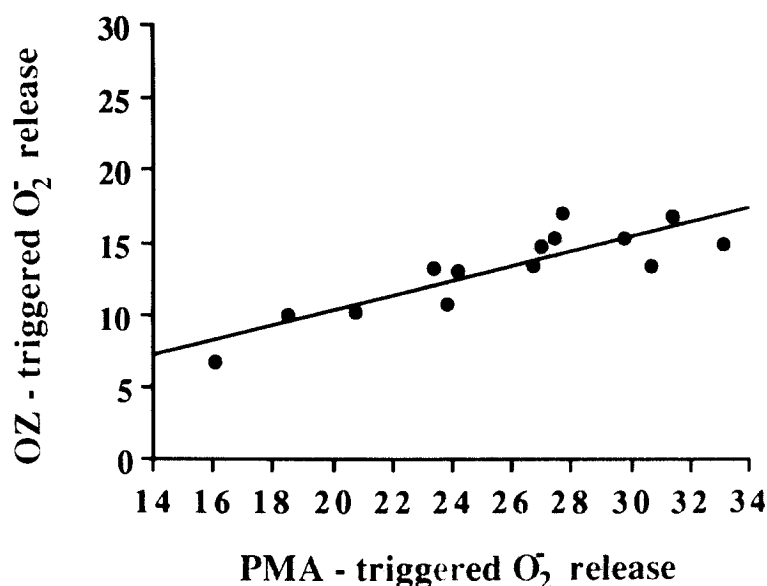


FIG. 2. Correlation between O₂⁻ production stimulated by PMA or OZ. For all patients tested (patients with AD and AR), OZ-stimulated O₂⁻ production was plotted against PMA-stimulated O₂⁻ production. Linear regression analysis reveals significant correlation between effects of these two distinct activators of NADPH oxidase ($r^2 = 0.759$; $p < 0.001$).

in AD. The exact mechanism for up regulation of CD23 on monocytes in AD is not known. However, it has been demonstrated that IL-4 is a potent inducer of surface CD23 on monocytes.¹⁷ Furthermore, there is evidence that patients with severe AD produce increased IL-4.^{18, 19} The matter may account for the increased IgE levels as well as the increased expression of CD23 on monocytes in AD.

The increased expression of CD23 could, in such cases, participate in the generation of increased O₂⁻ production by facilitating the interactions of IgE with monocytes. Indeed, rodent peritoneal macrophages and alveolar macrophages have been demonstrated to release lipid mediators of inflammation and proinflammatory cytokines on challenge with immune complexes containing IgE,^{20, 21} and the reactivity of alveolar macrophages from patients with asthma may depend on the interactions of these cells with IgE.²² IgE-dependent stimulation of human alveolar macrophages does not, however, elicit release of active oxygen species.²³

Second, the skin of patients with AD is heavily colonized with *Staphylococcus aureus*.²⁴ We have recently demonstrated that these staphylococcal species can produce toxins known to engage HLA-DR and induce interleukin-1 or tumor necrosis factor- α release.^{25, 26} Stimulation, by bacterial toxins, of the production of tumor necrosis factor- α by monocytes in the skin could therefore mediate this priming. This cytokine has indeed been demonstrated to play a role in priming of both monocytes-macrophages and neu-

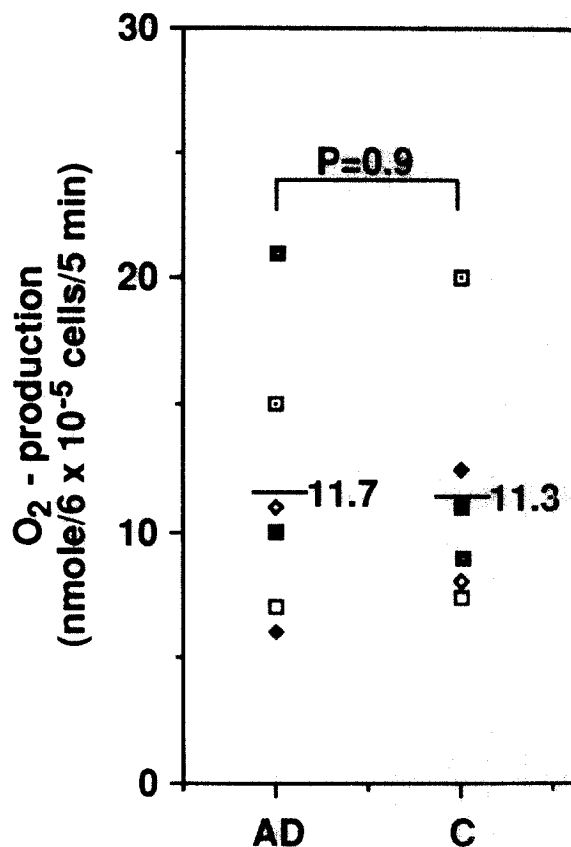


FIG. 3. Comparison of superoxide production after stimulation with PMA by peripheral blood neutrophils from patients with AD and control subjects (C). No significant differences in O₂⁻ production between patients with AD compared to that of control subjects ($p = 0.9$).

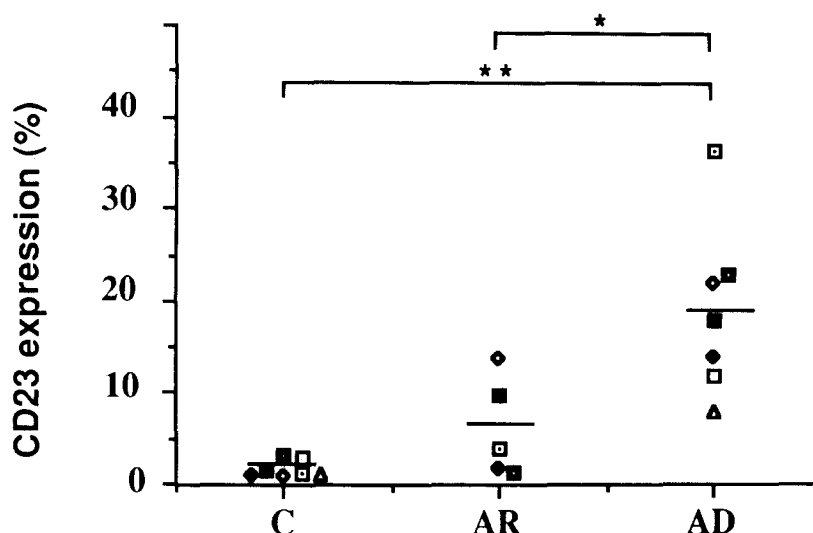


FIG. 4. Comparison of the percentage CD23-positive PBMs from patients with AR and AD and control subjects (C). Difference between control subjects and patients with AD was highly significant (**Scheffé F test, 12.46), as well as between patients with AD and AR (*Scheffé F test, 5.10). No difference between control subjects and AR.

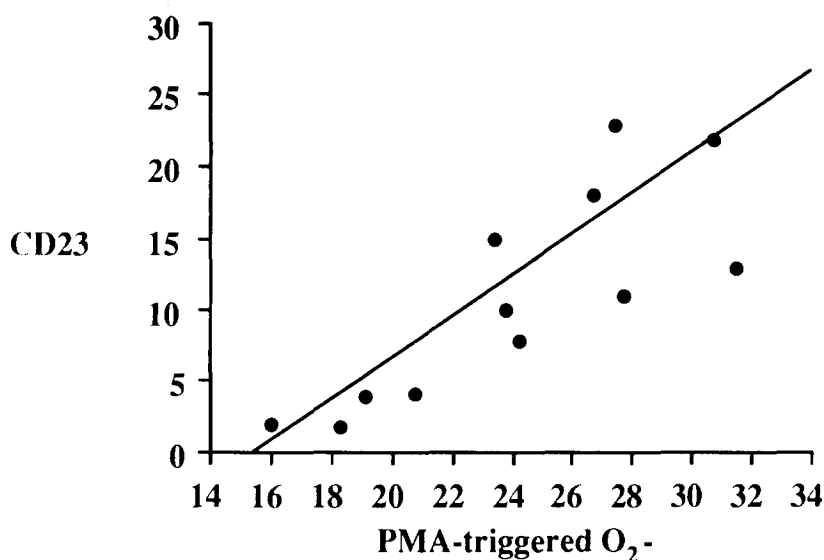


FIG. 5. Correlation between O₂⁻ production and CD23 expression by PBMs. For all subjects tested (seven patients with AD and five with AR), PMA-stimulated O₂⁻ production was plotted against CD23 expression. Linear regression analysis reveals significant correlation between these two functional and phenotypic markers of monocyte activation ($r^2 = 0.446$; $p = 0.01$).

trophils for O₂⁻ production.²⁷ In addition, other cytokines, such as granulocyte-monocyte colony-stimulating factor and interferon- γ that may be released during an inflammatory response have also been reported to prime monocytes in vitro for superoxide production.²⁸ Finally, endotoxins derived from gram-negative bacteria have been reported to prime the respiratory burst of monocytes-macrophages in vivo.²⁹

Bacteria in the skin could therefore participate both in priming and the direct activation of NADPH oxidase, for example, through phospholipase A₂-linked IgG or C3 receptors.

Previous studies have demonstrated that monocytes infiltrating into the skin of patients with AD bear CD23.^{3, 4} By extrapolation of our current results, which demonstrate a correlation between the expres-

sion of CD23 and monocytes priming for O_2^- generation, we suggest that infiltrating monocytes may contribute to the skin injury found in AD by increased production of reactive oxygen species. Indeed, the anti-inflammatory actions of corticosteroids in the treatment of AD may, in part, relate to the capacity of steroids to inhibit NADPH oxidase found in monocytes-macrophages.³⁰

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