orchestrate the production of NO in a major way.

When clearing occurs in psoriasis using a systemic drug[4], the lesions become less erythematous and clear from the inside out (V.B. Morhenn, unpublished). In regard to the immunostaining of inducible nitric oxide synthase (iNOS) in psoriatic lesions, clearly the labeling is associated with epidermal cells[5]. Unfortunately, double staining to differentiate LCs from KCs was not performed in this study, however, the results suggest that LCs are also stained!

Readiness to deal with wounds may explain the prevalence (~2%) of the 'psoriatic gene' in the American population. This frequency of the abnormal gene suggests that harboring it has survival value – psoriatic skin appears primed and ready to go if a bacterial infection occurs or a defect in the epidermis needs to be healed.

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References

1 Morhenn, V.B. (1997) *Immunol. Today* 18, 433–436
2 Morhenn, V.B., Weltman, H. and Waleh, N. (1995) *J. Invest. Dermatol.* 104, 609
3 Weller, R. and Ormerod, A. (1997) *Br. J. Dermatol.* 136, 136–137
4 Morhenn, V.B., Pregerson-Rodan, K., Mullen, R.H. *et al.* (1987) *Arch. Dermatol.* 123, 1633–1637
5 Bruch-Gerharz, D., Fehsel, K., Suschek, C., Michel, G., Ruzicka, T. and Kolb-Bachofen, V. (1996) *J. Exp. Med.* 184, 2007–2012

Crossreactivity of the T-cell receptor

In this issue of *Immunology Today*, Don Mason[1] argues that T cells should be highly degenerate in order to allow an immune response against any T-cell epitope. Because the number of possible epitopes is indeed much larger than the number of T-cell clonotypes in any immune system, we fully agree that each clonotype should recognize many epitopes. However, if the same degeneracy was expressed in terms of a precursor frequency, i.e. the fraction of clonotypes responding to any particular epitope, the T-cell immune response would seem to be specific. Moreover, a sufficient specificity is required because of self-tolerance. The demands of self-tolerance conflict with those of degeneracy, because crossreactive T cells are likely to become functionally deleted during self-tolerance induction.

Previous mathematical modelling has shown that this conflict can be solved at an intermediate crossreactivity[2–4]. The reasoning is based upon a crossreactivity parameter p – the chance that a particular clonotype recognizes a randomly chosen epitope (i.e. p corresponds to a naive precursor frequency). Calculating the repertoire size after self-tolerance induction (R), and the chance (Pi) to mount an immune response with this functional repertoire (see Fig. 1 legend) reveals that the 'optimal crossreactivity' to mount immune responses (see arrow in Fig. 1a) is determined by the number of self-epitopes that induce tolerance. The more self-epitopes inducing tolerance, the more specific the clonotypes should be to prevent their own deletion[2–4]. It was thus concluded that the degree of clonotype crossreactivity is largely determined by the need for tolerance to many self-antigens[2–4], rather than the need to respond to many pathogens, as Mason[1] argues.

The requirement of specificity becomes even stronger if one allows for incomplete self-tolerance induction (J.A.M. Borghans and R.J. De Boer, unpublished). Self-reactive clonotypes may escape the tolerance process and induce autoimmunity whenever they crossreact with an external pathogen[5], for instance due to mimicry[6]. We have developed a new model (see Fig. 1 legend) that incorporates this risk of cross-reactive autoimmunity. Tolerance to the ignored self is only maintained if none of the ignorant clonotypes are stimulated by a pathogen. The chance to survive a pathogenic attack (Ps) is a combination of the probabilities of immunity (Pi) and tolerance (Pt) (see Fig. 1). Comparison of the Ps curves of Fig. 1a and b shows that, in order to avoid crossreactive autoimmunity, clonotypes should be orders of magnitude more specific than was concluded previously[2–4]. If self-tolerance induction is incomplete, the optimal crossreactivity is no longer determined by the number of self-epitopes, and largely depends on the available number of clonotypes: large repertoires allow for

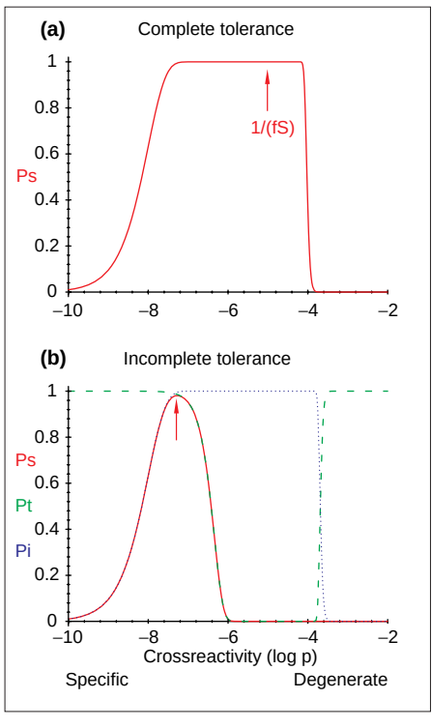

Fig. 1. *For the immune response to a single pathogen, the chance of surviving, Ps (solid red); the chance of mounting an immune response, Pi (dotted blue); and the chance of remaining self-tolerant, Pt (dashed green); are plotted as a function of the crossreactivity* (p) *of the clonotypes. Taking R0 as the repertoire size before tolerance induction, the number of clonotypes (R) surviving tolerance induction by a fraction* f *of all different self-epitopes (S) is* $R = R0(1 - p)^{fS}$. *The probability of immunity is* $Pi = 1 - (1 - p)^{R}$, *which has its optimum at* $p = 1/(fS)$. *The fraction of potentially autoaggressive clonotypes* (a) *that recognize at least one ignored self-epitope, is* $a = [1 - (1 - p)^{(1 - f)S}]$. *Only the fraction* p *of the autoaggressive clonotypes that are stimulated by the pathogen needs to be considered, thus the chance to stay tolerant is* $Pt = (1 - pa)^{R}$. *The survival chance (Ps) is the chance that the system remains tolerant to the ignored self less the chance that no immune response is triggered:* $Ps = Pt - (1 - Pi)$. *The arrows denote the maxima of the survival chances. Parameters are:* $S = 10^5$; $R0 = 10^8$; *and* $f = 1$ *(a) or* $f = 0.5$ *(b).*

highly specific clonotypes, reducing the chance of autoimmunity.

Our model demonstrates that the second conflict, between responsiveness to foreign epitopes and unresponsiveness to ignored self-epitopes, can in principle be solved by selecting for a sufficiently high lymphocyte specificity. For a mouse with 10^8 clonotypes (adopted from Ref. 1), 10^5 self-epitopes, of which 50% induce self-tolerance, and an optimal crossreactivity of $p = 10^{-7.28}$, we find a survival chance close to one (see Fig. 1). These numerical values, however, strongly depend on the specific choice of parameters, many of which are unknown. The mouse T-cell repertoire need not be as diverse as the estimated 10^8 clonotypes[1], which would result in a higher optimal p value. Furthermore, we have omitted from our model that additional tolerance mechanisms may silence autoreactive clones appearing during immune responses[7,8]. Moreover, there is no affinity in our model, and experimental estimates of precursor frequencies depend on the affinity cut-off of the particular assays. Taken together, the optimum of our model should not be interpreted as a quantitative prediction. Rather, our model suggests that the observed cross-reactivity of lymphocytes reflects a selection for the highest possible specificity within the specificity range allowing for sufficient immunity. High specificity avoids purging of the repertoire during self-tolerance induction[2–4], and avoids cross-reactive immune responses towards ignored self-molecules (J.A.M. Borghans and R.J. De Boer, unpublished).

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References

1 Mason, D. (1998) *Immunol. Today* 19, 395–404
2 De Boer, R.J. and Perelson, A.S. (1993) *Proc. R. Soc. London Ser. B* 252, 171–175
3 Whitaker, L. and Renton, A.M. (1993) *J. Theor. Biol.* 164, 531–536
4 Nemazee, D. (1996) *Immunol. Today* 17, 25–29
5 Ohashi, P.S., Oehen, S., Buerki, K. *et al.* (1991) *Cell* 65, 305–317
6 Zhao, Z.S., Granucci, F., Yeh, L., Schaffer, P.A. and Cantor, H. (1998) *Science* 279, 1344–1347
7 Ray, S.K., Putterman, C. and Diamond, B. (1996) *Proc. Natl. Acad. Sci. U. S. A.* 93, 2019–2024
8 Zinkernagel, R.M., Ehl, S., Aichele, P., Oehen, S., Kundig, T. and Hengartner, H. (1997) *Immunol. Rev.* 156, 199–209

Alternative non-steroidal anti-inflammatory therapy for asthma

In a recent issue of *Immunology Today*, Marone[1], and Spinozzi and colleagues[2] discuss interesting aspects of asthma. Marone gives an overview of recent advances and points out that, to date, asthma treatment has been based on conventional immunotherapy, corticosteroids and symptomatic treatment. Spinozzi *et al.* discuss the role of γδ T cells and allergen recognition in airway inflammation, stating that future management of allergic respiratory diseases should take into account recent experimental data on airway inflammation pathogenesis.

Asthma is now regarded as an inflammatory disorder involving several cell types and mediators. Corticosteroids have a pivotal role in asthma therapy[2], however, the resistance and toxicity related to their systemic administration has led to the assessment of other anti-inflammatory agents[3]. Here, in addition to the novel therapeutic strategies mentioned by Marone, I will comment on the potential role for non-steroidal anti-inflammatory therapy. Many such drugs have proved effective for several inflammatory and systemic autoimmune conditions such as rheumatoid arthritis, systemic lupus erythematosus, psoriasis, gout and allograft rejection.

In non-randomized, open trials, methotrexate, cyclosporin, orally and parenterally administered gold, intravenous immunoglobulin (IVIg), dapsone, and hydrochloroquine have all shown effects in asthma and might be able to reduce the patient's need for steroids[3–7]. Nevertheless, nearly all of these agents are associated with major side-effects, except IVIg: in this case, toxic effects are unusual but include anaphylaxis and a potential for viral transmission.

In placebo-controlled trials, only oral gold has produced modest steroid-sparing effects; inconsistent effects have been seen with methotrexate; no effect has been found with cyclosporin and colchicine[3,4,6,7]; and there have been no controlled studies as yet for IVIg, dapsone, hydrochloroquine and azathioprine. Before considering the use of such agents for their potential steroid-sparing effects, attempts should be made to lower steroid doses by intensive management of disease.

The efficacy of non-steroidal anti-inflammatory agents for steroid-resistant asthma remains to be established, since no study has specifically assessed such drugs in this subgroup of patients. Glucocorticoid resistance has been related to defects in DNA binding, a decrease in the number of corticosteroid receptors and decreased ligand-receptor affinity[8]. When a diagnosis of steroid resistance is well-established, unproven alternative asthma therapies may be tried, mainly through controlled and cooperative clinical trials.

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References

1 Marone, G. (1998) *Immunol. Today* 19, 5–9
2 Spinozzi, F., Agea, E., Bistoni, O., Forenza, N. and Bertotto, A. (1998) *Immunol. Today* 19, 22–26
3 Kane, G.C., Peters, S.P. and Fish, J.E. (1994) *Clin. Pulm. Med.* 1, 69–77
4 Alexander, A.G., Barnes, N.C. and Kay, A.B. (1992) *Lancet* 339, 324–328
5 Mazer, B. and Gelfand, E.W. (1991) *J. Allergy Clin. Immunol.* 87, 976–983
6 Fish, J.E., Peters, S.P., Chambers, C.V. *et al.* (1997) *Am. J. Respir. Crit. Care Med.* 156, 1165–1171
7 Erzurum, C., Leff, J.A., Cochran, J.E. *et al.* (1991) *Ann. Intern. Med.* 114, 353–360
8 Spahn, J.D., Leung, D.Y.M. and Szefler, S.J. (1997) *J. Asthma* 34,177–194