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Inverse correlation between the incidences of autoimmune disease and infection predicted by a model of T cell mediated tolerance

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Abstract

The contribution of pathogenic infections to the etiology of autoimmune diseases remains one of the outstanding problems in immunology. According to the classical concept of antigen mimicry, a direct correlation between the incidence of autoimmunity and infections would be expected. This view is supported by a few examples of autoimmune disorders, which are documented as being caused by infection with particular pathogens. In contrast, there are several experimental animal models where infection appears to prevent the onset of autoimmunity. Moreover, some epidemiological studies suggest an inverse correlation between the incidence of autoimmunity and infections in human populations. Here we propose a solution to this puzzle based on a theoretical model of tolerance driven by regulatory T cells. The concepts here developed delineate the conditions predicting an inverse correlation between the incidence of autoimmunity and exposition to common infections, and those in which antigen mimicry and inflammation of target organs have a role in the etiology of specific autoimmune disorders.
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1. Introduction

The increasing incidence of autoimmune and allergic diseases in wealthy countries with occidental style of life has been a clear and worrying trend in the last 50 years [1–3]. Possible causes for that trend range from changes in food and sedentary habits, to environmental chemical contamination, to stress due to faster rhythm of daily life. However, it is difficult to quantify properly those factors, and hence how much they contribute to that trend cannot be easily estimated for correlation purposes in populations with different incidences of autoimmunity.

More recently, a different view has emerged that relates the incidence of autoimmune diseases to the relative cleanliness of the immediate environment [4,5]. Although there is no solid rationale for this view, it is supported by two independent lines of evidence. On the one hand, there are several epidemiological reports of a north/south gradient for the incidence of autoimmune diseases in normal resident [6–9] and immigrating [10,11] human populations, which is inversely correlated with the prevalence of some infectious diseases [5]. On the other hand, there are several experimental animal models where the onset of autoimmune syndromes is prevented by particular infections [12–14] or by rearing autoimmune-prone animal strains in conventional conditions instead of specific pathogen free or germ free conditions [15,16]. As a whole, these observations hinted at a "hygiene" hypothesis [17] according to which common infections may have a role in preventing autoimmunity.

Interestingly, the hygiene hypothesis seems to contradict the canonical view of autoimmunity as caused by the cross-reactivity of a microbial antigen and some host-antigen in the course of infection (antigenic mimicry [18]) or as a consequence of pathogen-induced inflammation at the target organs [19,20]. These latter hypotheses would naturally predict a direct correlation between the incidence of autoimmunity and infections. Epidemiological studies have suggested such an association for some specific autoimmune diseases [6] and,

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further, antigenic mimicry has been documented in a few of these cases—notably, streptococcal miocarditis [21], Lyme arthritis [22], rheumatoid arthritis [23]. A deeper analysis revealed, however, that it is far from well established in most autoimmune disorders [24,25]. Nevertheless, the canonical view is also supported by different animal models in which specific, pathologic autoimmune responses are triggered by experimental infections or proinflammatory adjuvants (reviewed [26]); or in which spontaneous [27] or iatrogenic [28,29] autoimmune syndromes are favored by commensal or infectious microorganisms.

The apparent paradox that infection may be causing and preventing autoimmune diseases demands a deeper understanding of the mechanisms mediating natural tolerance to host-antigens. Natural tolerance has been proposed to involve a continuous and active process, because clonal deletion in primary lymphoid organs is relatively inefficient in purging the lymphocyte repertoire of self-reactivities [30]. A paradigm of the basis for this active and continuous tolerance activity that is gaining rapidly a prominent status is that of regulatory T cells [31], and specifically CD4+CD25+ T cells [32]. These regulatory T cells are naturally generated in the thymus in a manner strictly dependent on major histocompatibility complex (MHC)-Class II expression by cortical thymic epithelial cells [33], and they suppress the activity of other potentially pathogenic auto-reactive T cells both in vivo and in vitro [34,35]. Recently, we have developed a mathematical model to assess the role of these regulatory cells in natural tolerance [36–38]. In the present study, the etiology of autoimmunity predicted by this model is explored. The results show that a view of natural tolerance based on regulatory T cells can provide a simple rationale for an inverse correlation between the incidence of autoimmunity and infections, yet accounting also for the potential role of antigen mimicry in the etiology of some particular autoimmune disorders.

2. The model and its basic properties

Our model considers the dynamics of three mutually interacting cell populations [36]: (a) antigen presenting cells (APCs) displaying MHC-self-peptide complexes at the membrane; (b) proinflammatory autoreactive T cells (P) that can potentially provoke autoimmunity; and (c) regulatory autoreactive T cells (R), which suppress proinflammatory T cells. See Appendix A for a mathematical formulation. Three basic assumptions are made in this formulation. First, interactions between P and R cells require the formation of multicellular conjugates with APCs (Fig. 1). Second, the R cells inhibit the proliferation of P cells at the APC surface and do not proliferate when stimulated with APCs alone (Fig. 1, panel A). This is in agreement with many experimental observations (reviewed in [32]) and has been justified elsewhere [36,37]. Third, the population of R cells expands by P-cell dependent cell proliferation as suggested by recent experimental data [39,40]. Finally, immunity and tolerance are interpreted, respectively, as the competitive exclusion of R cells by the expansion of P cell population and the coexistence of both R and P cell populations at equilibrium.

It has previously been shown that the particular dynamical behavior set into play in this model is determined by two key composite parameters, $G_R=K_R\ \mu\ A/d$ and $G_P=K_P\ \pi\ A/d$, which represent the effective "growth indexes" of R and P cell populations respectively [36]. These growth indexes are directly proportional to the number of APCs (A), to the strength of the conjugation between the APCs and the T cells (respectively K_R and K_P for regulatory and proinflammatory cells), and to the maximal growth rates of the R and P cells (respectively μ and π). They are inversely proportional to the death rate of T cells (d). These two parameters define three regions in the parameter space according to the resulting dynamic behavior (Fig. 2). For parameter values in region I the system evolves always to an equilibrium state in which there are no R cells, irrespective of the initial proportion of P and R cells. Therefore, in this parameter region autoimmunity will always emerge spontaneously in the system. Parameter region II is characterized by an equilibrium state in which the population of R cells controls the expansion of the P cell population, independently of the initial proportion of P and R cells. Here a stable tolerant state is always obtained in the system. Therefore, in this parameter regime autoimmunity could not emerge in the system. Finally, in parameter region III the system is bi-stable, meaning that either the state in which no R cells are present (autoimmune disease) or the state in which P and R cells coexist in stable balance (tolerance) can be reached depending on the initial proportions of P and R cells. In this parameter regime the system can develop into a stable tolerant state. Although autoimmunity may be induced in this state upon appropriate perturbations, healthy immune systems necessarily operate on the bi-stable regime of region III [36]. This is the only condition compatible with the observations that healthy animals have significant numbers of both R and P cells, and that the incidence of autoimmune pathology or tolerance can be modulated in recipients adoptively reconstituted with different proportions of P and R cells. Furthermore, when many P and R cell sub-populations differing in their antigen specificities were considered [38], only parameter values within region III lead to tolerance to host-antigens while retaining the capacity to mount specific immune responses to infectious agents. In summary, inside region III a trade off between two opposite selecting forces determines the optimal

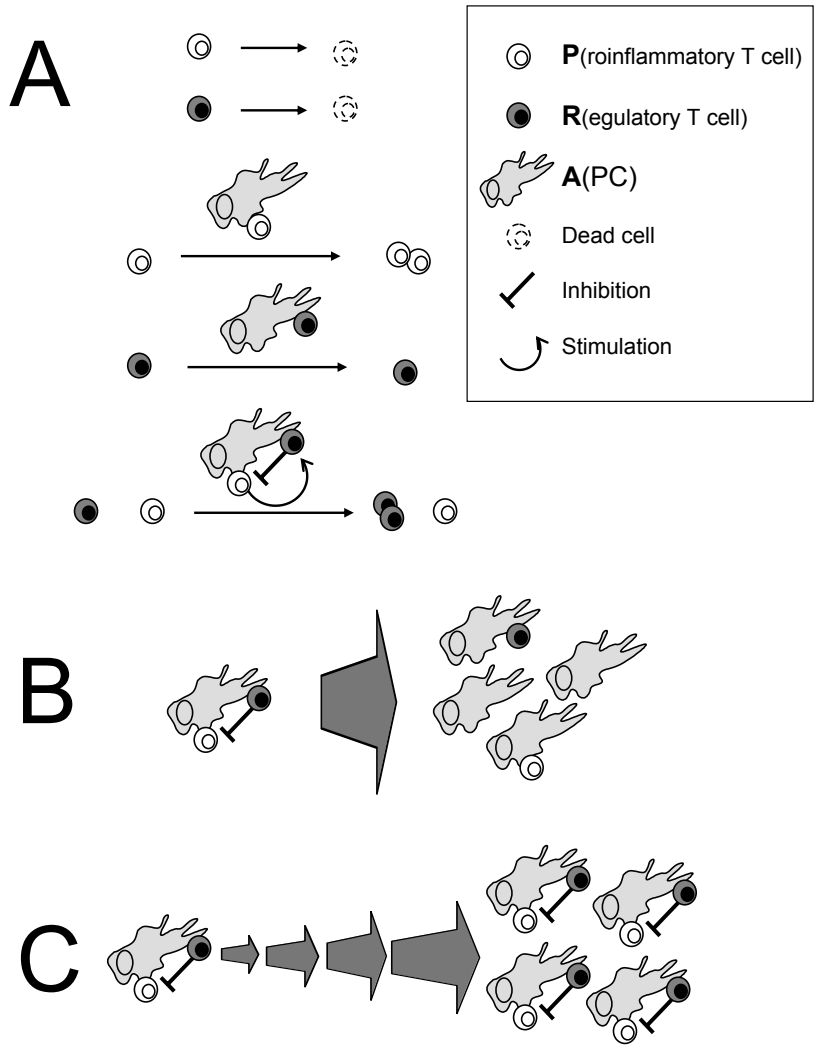

Fig. 1. Illustration of the model of T cell mediated tolerance. A, Basic processes and interactions involving regulatory cells, proinflammatory cells and APCs. B, A fast and large increment in the number of APCs "dilutes" the interactions between regulatory and proinflammatory cells, and leads to the onset of autoimmunity. C, A slow stepwise increase in the numbers of APCs allows the adaptation of the regulatory cell population size, and reenforces tolerance.

relationships between model parameters. On one hand, there is the need to minimize the risk of autoimmunity, which requires being as far as possible from region I. But, on the other hand, there is the need to minimize the susceptibility to infections, therefore to maximize the system's reactivity, which implies being as close as possible to the interface with region I. Thus, in this theoretical framework as in those proposed by others [41,42], the risk of autoimmunity is the price that must be paid for assuring immune responses to pathogens.

We have also studied a model variant in which the interaction between P and R cells promotes the growth of regulatory populations by an R-dependent conversion of P cells to the regulatory phenotype [36]. This conversion of P cells was originally proposed by Qin et al. [43] and more recently brought into attention by studies of human regulatory T cells [44,45]. The model presented here and the variant with conversion of P cells display the same qualititative behaviour. Further, the same behaviour was also recovered in computer simulations of many different clones of both P and R cells (for a description of this kind of simulations see [38]) being in this sense rather generic.

3. Results

3.1. Genetics of autoimmunity

Autoimmunity could result from genetic defects, and indeed genetic associations have been largely observed in the etiology of autoimmune disorders. In the model, genetic factors should affect in a combined and effective

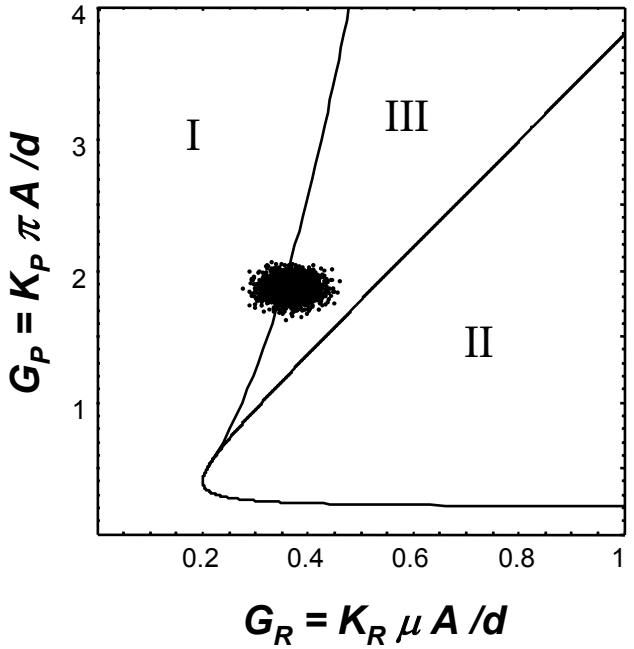

Fig. 2. Bifurcation diagram of the model behavior as function of growth indexes of regulatory and proinflammatory cell population, respectively G_R and G_P. Areas labeled I, II and III correspond to those parameters values for which the model predicts, respectively, spontaneous autoimmunity, non-specific tolerance (to self as well as to microorganisms), and possibity for self-tolerance and resistance to microorganisms. Each dot represents an individual of a genetically diverse population. The fraction of autoimmune-prone individuals in the population is computed as the fraction of dots within region I.

way the different parameters controlling essential properties of the system dynamics. Therefore, the different genetic variations in a given population will be reflected in effective variations of the parameters G_R and G_P between individuals of that population. Let us assume that these two parameters are independent phenotypic characters distributed normally around respective averages $\langle G_R \rangle$ and $\langle G_P \rangle$, with variances V[G_R] and V[G_P]. Following the analysis of the previous section, the mean parameter values for any normal population must be somewhere inside region III, but genetic variation, if large enough, may locate some individuals of the population into regions I and II (Fig. 2). Therefore in the population there may always be a fraction of individuals that spontaneously develop autoimmune disorders. This fraction can be estimated in the model from the fraction of the 2D Gaussian distribution of the parameters G_R and G_P (dots in Fig. 2) whose values are in the autoimmune region I. Given the fact that G_R and G_P are composite parameters, many different classes of genetic susceptibilities to autoimmunity can be identified according to the model behaviour. These susceptibilities would correspond to any change on a parameter resulting in a displacement of the position of an individual in the diagram of Fig. 2 closer to region I. Noteworthy among them are: (1) defects in T lymphocyte proliferation kinetics promoting either a higher division rate for P cells (large p) or a lower growth rate of R cell population (low values of μ); (2) defects in the death rates (d) of P and R lymphocytes; and (3) defects in the repertoire selection in the thymus, affecting the antigen-specific conjugation of T cells with APCs that present host-antigens (larger K_P or lower K_R). Moreover, the dependence of composite parameters on the different factors outlined above allows predicting how they may complement or counterpoise, on their contribution to an autoimmune phenotype. Clearly, a combination of small defects in several of those factors can be equivalent to a single large defect in determining an autoimmune phenotype; and alternatively variations in one genetic factor (i.e., changes in the value of a given parameter) can compensate a variation in other factor, leading to a normal phenotype. Thus, according to the model the contribution of genetic factors to the etiology of autoimmunity is most likely epigenetic.

3.2. The role of infections in triggering autoimmunity

Infection with a fast growing microorganism stimulates the immune system (specially the innate immune system) provoking a rapid burst of APCs in the place of infection by recruitment, differentiation and proliferation of APC precursors. Much of these APCs at the site of infection will be processing and presenting the foreign antigens associated to the invading microorganism. However, as a side effect of inflammation the number of self-antigen determinants presented will be also moderately increased above their basal levels. Therefore, in our model, which only considers auto-reactive P and R cells dynamics, infections are assumed to provoke an increment in the number of APCs presenting self-antigen determinants. If the invading microorganism does not bear antigenic mimicry with the self-determinants recognized by P and R cells then the increment in self-Ag presenting APCs will rely only on bystander stimulations and hence will be moderate. But if there is antigen mimicry the R and P cells will also recognize those APCs presenting the microbial antigens and therefore the net increment of APCs stimulating self-Ag specific T cells may be rather large.

In the model, any perturbation leading to an increment in the number of APCs alters the system dynamics, depending on the particular values of parameters G_P and G_R used in the simulations (Fig. 2) and on the strength of the applied perturbation. For parameters within parameter region I the system always develops to the autoimmune state, independently of the external perturbation. For parameters within regime II the system always evolves to the tolerant state and, no matter the perturbation applied, it will always return rapidly to this state (data no shown). However, for parameters within

regime III an increment in the number of APCs (A) that goes above a given size and speed threshold will make the system switch from the tolerant to the autoimmune state. This property is illustrated in Fig. 3, for a particular perturbation of a tolerant system. There, the number of APCs is increased from the basal value A_0 to the value A_m according to a logistic growth with kinetic constant v (see Appendix B). A fast increase of the number of APCs (Fig. 3A) leads to a sustained expansion of the P cells and, subsequently, to the breakdown of tolerance. The same net change in the number of APCs, but with a slow kinetics (Fig. 3B) does not break tolerance, entailing only a transient expansion of the P cells, which is controlled by the subsequent expansion of the R cells. Breaking tolerance in the system requires also, a minimal net increase in the number of APCs and the slower the APCs increase (lower values of v) the higher the minimal increment required (Fig. 3C). Moreover, within parameter region III the minimal increment required to break tolerance depends also on the particular values used for G_P and G_R. The closer these parameters to the interface with region I the lower the minimal increment required to break tolerance.

The latter property of the model provides a simple explanation for the induction of organ specific autoimmunity by local infections bearing antigenic mimicry [46]. However, the role of mimicry in this model is to amplify the perturbation that any infection provokes on the immune system. Therefore the model predicts that infections that do not bear antigen mimicry but induce a sufficiently large inflammation might also result in autoimmunity. Moreover, any substance (for instance adjuvants) that potently stimulates the innate immune system, increasing the level of antigen presentations, might induce a similar effect. Thus, the model also explains the results of several animal models where autoimmune events are induced by immunization with tissue-antigens in adjuvant or even with adjuvant alone (reviewed in [47]). Interestingly, the model suggests that the transitoriness of the autoimmune events commonly induced in these animal models results from a "weak" perturbation, i.e., a perturbation leading to a transient expansion of pathogenic cells that is controlled by the subsequent expansion of the R cells, and hence that does not fully break tolerance (similar to the dynamics shown in Fig. 3B).

Summarizing, in the model healthy individuals in region III can be always driven to autoimmunity upon a perturbation inducing a sufficiently large and fast increment in the level of self-antigens or self-crossreactive foreign antigens presented by APCs, as provoked for instance by some infections. But the minimal level of this perturbation required to trigger autoimmunity in this region increases with the genetically determined distance to the interface with region I. Thus, at the population level the model provides a rationale for the observation

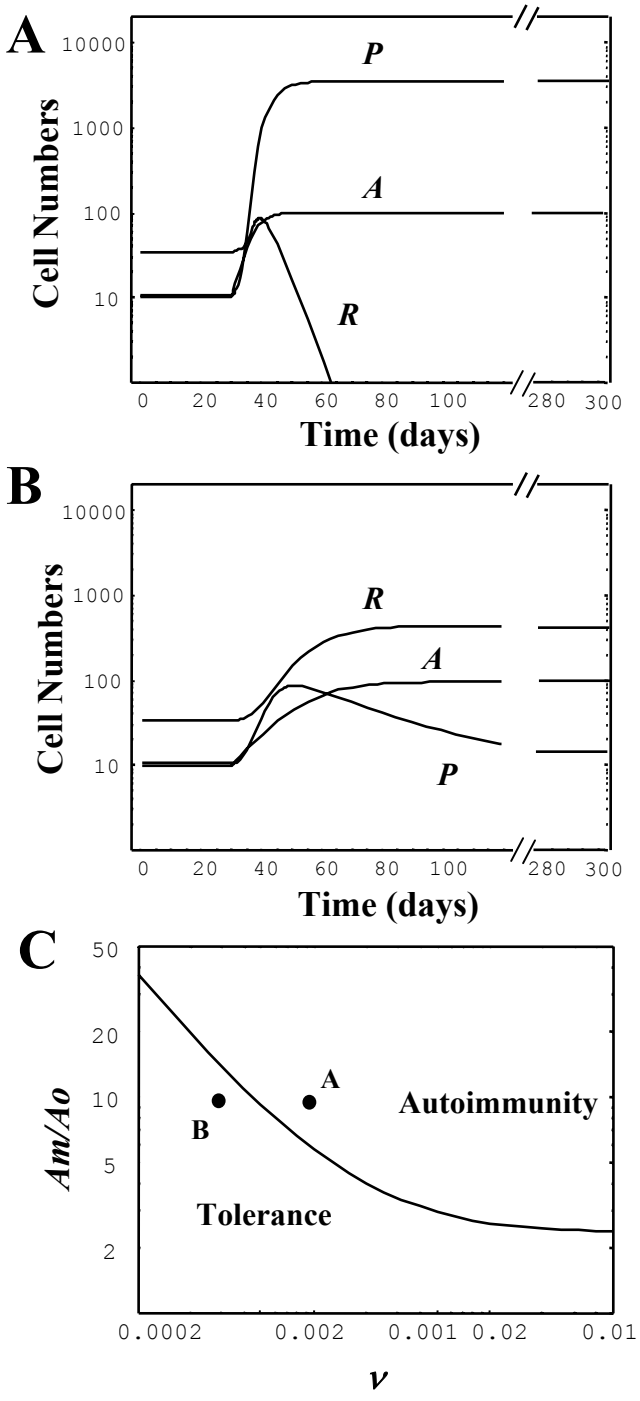

Fig. 3. Effect of increasing the number of APCs in the model. A and B show the typical time courses of the number of P and R cells following the perturbation of a stable tolerant state by increasing the number of APCs (from A_0=10 to A_m=100). A faster increase in APCs (v=0.0025 d^{-1}) leads to a switch from the tolerant to the autoimmune state (panel A), while a slower increase (v=0.0005 d^{-1}) induces only a transient expansion of the P cells, which is controlled by the ensuing expansion of the R cells, without breaking the tolerant state (panel B). C, Relationship between APC growth rate (v) and maximum relative APC increase (A_m/A_0) resulting in either tolerance or autoimmunity. The line represents the boundary between both behaviors. Dots labeled A and B correspond respectively to the cases shown in panels A and B. The particular parameters in these simulations were: d=ln(2)/72 h^{-1}; π=ln(2)/12 h^{-1}; s=5; K_P=K_R=0.3; μ/d=0.35.

that some infections can induce autoimmunity and that there are genetic factors rendering individuals more or less susceptible to such induction of autoimmunity.

3.3. Effect of common infections on autoimmunity

Infections that provoke autoimmunity are rare. Common bacteria and viruses usually stimulate immune activity without provoking autoimmunity, perhaps due to the absence of antigenic mimicry or because they do not induce a sufficiently large or fast inflammation. However, the frequent exposition of an organism to infections may have important effects on the basal behavior of its immune system. To model those effects, the particular ways by which infections may affect the basal immune system activity to self-antigens have to be specified. Two biologically reasonable scenarios are analyzed in what follows, pinpointing the conditions under which an inverse correlation between the incidence of infections and the incidence of autoimmunity is predicted by the model.

In the first scenario, following the reasoning in the previous section, frequent sub-clinic infections with different microorganisms are assumed to stimulate moderately the host's innate immune system, each contributing indirectly to the enhancement of self-antigen presentation. Therefore, individuals developing and living in an environment with a higher incidence of infections will have a higher mean level of presentation of host-antigens. However, either because such increment in self-antigen presentation occurs by small increments (Fig. 1C), resembling the process simulated in Fig. 3b, or because it takes place during self-tolerance induction in the perinatal period, it will not directly cause autoimmunity. Moreover, as will be demonstrated below, it will lead to the opposite effect, reinforcing the tolerant state of the individual. This scenario can be modeled, in a simple way, assuming that the average number of APCs presenting host-antigens per individual (A) has a genetically determined basal level (A_0) and increases proportionally to the incidence of infections, I, in the population (see item A in Appendix C). This implies that the values of G_R and G_P will depend on the incidence of infections. Thus, in the model, the same individual (or individuals with identical genetic make up) developing in environments characterized by different incidence of infections will be located at different positions of the parametric space of Fig. 2. More specifically, the point that represents a given individual lies in the straight line crossing the zero and the basal position of that individual (G^0_R, G^0_P) i.e., its position in the absence of infection (see Appendix C). The particular position depends on the actual value of A. The higher the incidence of infections, the higher the value of A and the farther this point will depart from its basal position (G^0_R, G^0_P) toward higher values of G_R and G_P. Consequently, the assumed 2D-Gaussian distribution of parameters G_R and G_P in a host population will be located deeper into the parameter region III for higher values of the incidence of infections index I (see Fig. 4A). Therefore, the frequency of autoimmune individuals will be lower than expected were that population living in the absence of infections. In other words, assuming that frequent, subclinic infections result in a stepwise increase in the number of APCs presenting host antigens, the model predicts an inverse correlation between the incidence of autoimmunity and the incidence of infections (Fig. 4B).

The second scenario assumes that, during an infection, the specific response to the invading microorganism induces a bystander expansion of autoreactive R and P populations. This bystander effect would follow, for instance, an intense release of cytokines or co-presentation of host and pathogen antigens by the same APC in inflammation foci. Different infections may have even or biased side-effects on P and R populations, as suggested by the observation that different microorganisms can target different classes of specific T cells indirectly via the APCs [48,49] (or even directly [50]) perhaps due to their expression of specific molecular patterns recognized by the innate immune system [51]. Net effects of bystander stimulation by subclinic infections can be incorporated in the model by assuming that they result in a fractional increase of the growth indexes of P and R cell populations that is proportional to the incidence of infections (see item B Appendix C). Proportionality constants β_P and β_R for the respective growth rates of pathogenic and regulatory cells allow for accommodating generically different microorganism-dependent biases. A ratio β_P/β_R equal to unity corresponds to an unbiased stimulation of autoreactive P and R cells; when this ratio is lower than 1 there is a preferential stimulation of regulatory cells; and when it is greater than 1 there is a preferential stimulation of pathogenic cell types. Under these assumptions, the point representing in the parametric space of Fig. 2 an individual living in an environment with incidence of infections I will lay in a straight line that pass through its basal position in the absence of infections (G^0_R, G^0_P), and whose slope is given by $(\beta_P/\beta_R)\times(G^0_P, G^0_R)$ (see Appendix C). The higher the value of I the farther the position of the individual will depart form its basal position toward higher values of G_P and G_R. Consequently the ratio β_P/β_R controls the position of the population in the parametric space (Fig. 4C) as a function of the incidence of infections I in the immediate environment and therefore control the relation to the incidence of autoimmunity in the population. For $\beta_P/\beta_R=1$ the model always predicts an inverse correlation between the incidences of autoimmune diseases and common infections (Fig. 4D). For higher values of β_P/β_R the model predicts a biphasic behavior, meaning that there is an inverse correlation for high incidence of

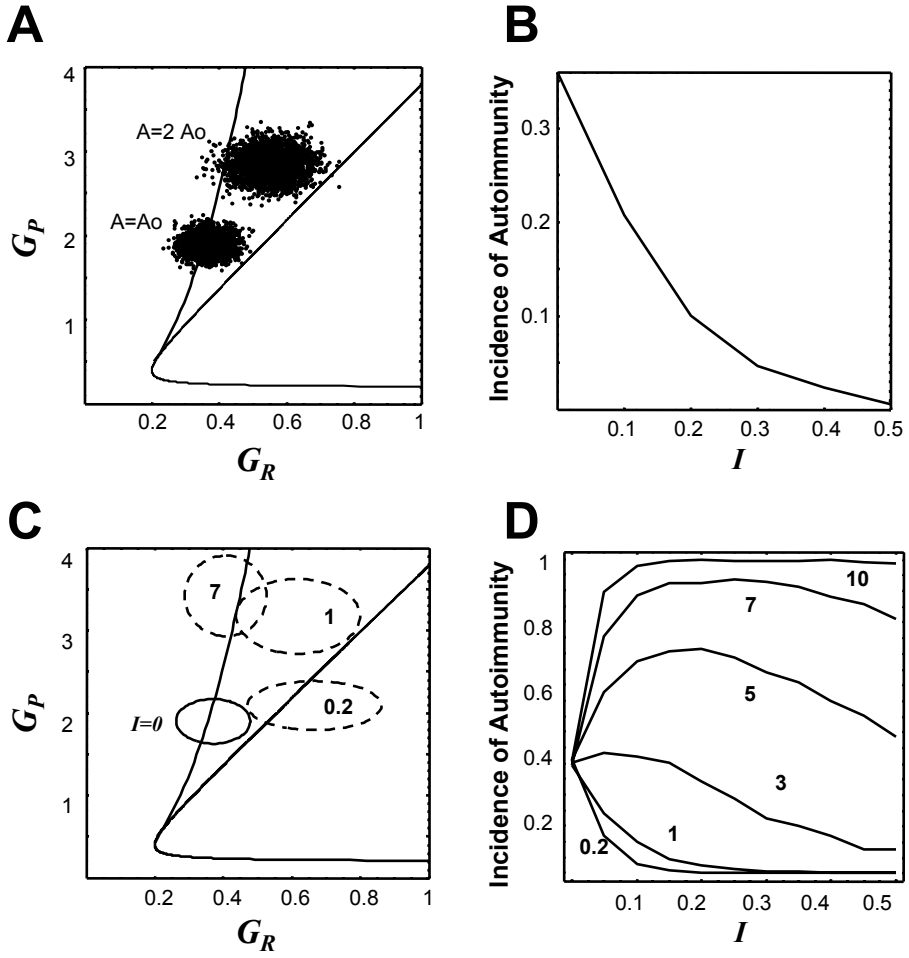

Fig. 4. Effects of common infections on the incidence of autoimmunity in the model. A and B correspond to the scenario in which common infections increase the numbers of APCs presenting host-antigens. A, The two clusters of dots represent the same population in two different environments, one with no infections (I=0, A=A_0) and the other environment with infection (I=0.25, A=2 × A_0). B, Predicted relationship between the incidence of infections and the incidence of autoimmunity according to this scenario. C and D correspond to the scenario in which common infections induce bystander stimulation of proinflammatory and regulatory cells increasing their growth rate with a relative strength given by the ratio β_P/β_R. C, The location in the (G_R, G_P) parametric space of the different individuals changes in this scenario, as the incidence of infections increases, in an overall direction that depends on the value of β_P/β_R. Circles are contour lines of the same, genetically diverse population, comprising 90% of the individuals. Solid circle corresponds to the absence of infections (I=0). Dashed circles were obtained for I=0.25 and the indicated values for the ratio β_P/β_R. D, Predicted relationship between the incidence of infections and the incidence of autoimmunity, according to this scenario, for the indicated values of β_P/β_R.

infections and a direct correlation for low incidence of infections (Fig. 4D, cases 3 to 7). Only for very high values of β_P/β_R the model predicts always a direct correlation between the incidence of autoimmunity and infections. Therefore, in this scenario, the model will predict an inverse correlation between autoimmunity and infections, unless a preferential bystander stimulation of P cells over R cells is assumed to be the rule.

Moreover, it is very likely that in most instances the above two scenarios take place simultaneously. In that case, any bias towards P-cell bystander stimulation will be counteracted by the increase in APC numbers, broadening the range of values of β_P/β_R for which the model predicts an inverse correlation between the incidence of autoimmunity and infections (data not shown).

Finally, it is important to note that the results reported in this section are completely generic and independent of the particular shape and initial position of the population distribution assumed in the calculations. In other words, different distributions for the G_P and G_R values that characterize each individual in the absence of infections result in the same relationships between the incidence of infections and autoimmunity. These results are just determined by the geometry of the interfaces between parameters regions I–III and II–III, as well as the parameter relationships defined by composite parameters G_P and G_R. In turn, such properties of the model are strictly a consequence of the postulated mechanism of interactions between P and R cells.

4. Discussion

We have analyzed here a model of T cell mediated tolerance, previously developed for individual hosts, in the more general context of the genetic/epidemiological domain at a population level. This provided a new theoretical way to approach the paradoxical observations that infections may elicit specific autoimmune diseases under some circumstances but that the average microbial load may protect (non-specifically) against autoimmune pathologies. Our present analysis suggests a solution to this puzzle, which resides in the way microorganisms engage the individual hosts and alter the parameters determining the dynamics of regulatory and proinflammatory autoreactive cells. Particularly, we show that infections bearing significant antigenic mimicry could induce autoimmunity if they entail acute inflammation, which substantially increases the antigenic presentation of the determinant involved in the mimicry. But if common infections lead to small increases in presentation of self-antigen determinants or lead to a similar bystander expansion of the regulatory and pathogenic T cells, then frequent infections would prevent autoimmunity. Therefore, the theoretical framework explored here predicts a direct correlation between the incidence of some specific autoimmune disorders and some particular infections, and an inverse correlation between the incidence of most autoimmune disorders and the incidence of common infections.

These opposing consequences of host-microbial relationships stem in the model from the non-linearity of the mechanism underlying tolerance. Particularly relevant are the postulates that suppression of proinflammatory cells by regulatory cells requires direct interactions while conjugated on the same APC (or more generically, while activated in the same inflammation-dependent niche), and that regulatory T cell populations depend on proinflammatory cells to grow. We notice that the second postulate is necessary but not sufficient because it will predict the protective effect of infections on autoimmunity but fails to explain how acute infections and inflammation could trigger autoimmunity. The latter property requires that a fast increase in the number of APCs and/or size of inflammation-dependent niches [52] will decrease the inhibitory interactions between regulatory cells and proinflammatory cells. Analysis of a suppression model in which the APC conveys a regulatory signal from the regulatory cell to the proinflammatory cell (as suggested in [53–55]) indicates that also in this case a fast increase in APCs can trigger autoimmunity (our unpublished results). However, in models of suppression where activated regulatory cells non-specifically suppress proinflammatory cells (as proposed in [56]) is more difficult to envisage how acute infections could trigger autoimmunity (our unpublished results).

So far we have been concerned on how an acute infection could trigger an autoimmune disease and we have neglected the question on whether the disease will be transient or chronic. Our model predicts that if the infection is rapidly resolved and the normal numbers of APCs are suddenly restored then tolerance will be reestablished. However, if the infection is only slowly controlled and the APCs return to their baseline numbers in a slow pace then autoimmunity could become chronic. For a detailed analysis of the conditions for reestablishment of tolerance upon a transient infection causing autoimmunity the reader is referred to [38]. Here we have also assumed that the dynamics of autoreactive T cell populations would be affected by responses to infectious agents but have neglected how the regulation of autoreactivity could affect immune responses. This is a fundamental issue that was partially addressed elsewhere [38] and which we are developing further.

The growth and persistance of regulatory cell populations are strictly dependent on proinflammatory cells in our model. This postulate is grounded on both theoretical results [36,37] and in vitro observations [39,40] and it is compatible with the observation that CD4+CD25+ T cells expand in adoptive transfers [57] since this subset is most likely not pure in regulatory cells and contains also non-regulatory CD4+CD25+ activated T cells. However, recent reports indicate that upon microbial activation dendritic cells can produce IL-2 [58,59], which is a resource for regulatory T cells [60,61]. How would such extra growth resource change our model? We can anticipate that if the source were relatively small it will hardly change the model behaviour. However, if the source were very large then it could subvert the balance between regulatory and proinflammatory cells. The latter scenario is unlikely in normal conditions but it might appear in pathologic situations with genetic or infectious basis, which could result in generalized immunodepression.

Our analysis makes some predictions that could be studied experimentally, providing thus a test for the theoretical framework proposed here. In this sense, the most striking proposal of our model is that a sufficiently large enhancement in self-antigen presentation (increment in the number of APCs in the simplest case) would induce or prevent autoimmunity when conducted respectively with a fast or slow kinetics. This prediction can be tested experimentally, using animal models that spontaneously develop some particular autoimmune disease, but in which the disease incidence is graded. For instance, inoculating NOD mice with APCs from the spleen of non-treated NOD mice, using different doses and time dependent schedules in this treatment, and checking the frequency of animals that develop diabetes. Our model predicts that treatments including a large inoculum with those APCs would accelerate the onset of diabetes; but those treatments including several inocula

with relatively small amounts of APCs would delay or prevent the development of the disease. Furthermore, in order to test whether or not an expansion of regulatory T cells is involved in the observed outcome, the above experimental setting could be complemented by adoptively transferring different T-cell populations from the animal groups receiving different APC treatments, into immuno-deficient (lacking T cells) NOD mice.

The genome of host populations may be adapted to common microorganisms present in the population's usual environment by selection of alleles that compensate phenotypically the effects of microbial load and optimize the trade-off between defensive immunity and tolerance. Populations adapted to different environments would be expected to have genomes differing in their contribution to parameters G_P and G_R. Thus, the basal, genetically determined values of G_P and G_R may be lower in populations adapted to environments with high infection prevalence and diversity than in populations living in environments with low infection prevalence or diversity. Recent immigrants from the first population would be more prone to autoimmunity in the "cleaner" environment of the second population. It is tempting to relate this scenario to the documented observation that the incidence of autoimmune pathologies is higher in immigrants of African or Afro-Caribbean origin in the United Kingdom than in the resident population [62]. Notwithstanding its potential interest, this hypothesis raises more questions than answers. For instance, what is the rate of adaptation of populations by negative selection on autoimmune individuals? Significant reduction of infection prevalence in Western Europe has taken place in the last century, raising the question on whether the rate of adaptation of resident populations is enough to justify the differences observed between the prevalence of autoimmunity in residents vs. immigrants. An alternative explanation is that recent emigrants are faced to an entirely new group of microorganisms that trigger in them strong immune responses to self-crossreactive antigens, which according to our model would trigger autoimmunity.

Finally, genetic studies of autoimmune diseases typically implicate tens of candidate loci in a complex causal pathway [63–68]. Assigning a causal role to disease-associated genes is necessary to understand their effects and to design therapeutic approaches. This assignment requires the previous identification of a corresponding phenotypic trait. However, the association techniques are essentially silent in this respect. Our mechanistic model could have operational value in this task, since it identifies not only a few traits as being a priori the most likely candidates, but also the operational/mechanistic conditions that associate them to disease propensity or protection. For example, genes involved in lymphocyte proliferation or survival are obvious candidates. Furthermore, those alleles that increase lymphocyte growth indexes (G_P and G_R) are good candidates for disease protection, while those decreasing growth are candidates for disease-propensity.

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Appendix A. A model of the dynamics and interactions of T cells involved in natural tolerance

We model the dynamics of proinflammatory P cells and regulatory R cells that recognize a homogeneous population of APCs. Interactions between P and R cells require formation of multicellular conjugates with APCs, and each APC contains s independent sites for cell conjugation (Fig. 1). It is assumed, on the one hand, that a single R cell at the surface of a given APC inhibits the activation and proliferation of every P cell that interact with this APC. On the other hand the interaction between P and R cells promotes the growth of the regulatory population by a P-dependent proliferation of R cells. The equations describing the model are:

$$\frac{dP}{dt} = \sum_{i=1}^{s} \pi \times i \times A_{i,0}(P_c, R_c) - d \times P_f \tag{1a}$$

$$\frac{dR}{dt} = \sum_{i=1}^{s} \sum_{j=1}^{s-i} \mu \times i \times j \times A_{i,j}(P_c, R_c) - d \times R_f \tag{1b}$$

where:

P, R	Total number of P cells and R cells at any given instant t
$A_{i,j}(\ )$	Number of multicellular conjugates containing an APC conjugated to i P cells and j R cells
A	Total number of APCs
P_c, R_c	Number of P and R cells conjugated with APCs

P_f, R_f Number of free P and R cells, given by $R_f=R-R_c$ and $P_f=P-P_c$
S Maximum number of T cells that can conjugate simultaneously with an APC
D Death rate of P and R cells
π Proliferation rate of P cells
μ P-cell dependent growth rate of the regulatory population

The number of multicellular conjugates of a given type are obtained, following our previous study [36], as the product of two hypergeometric functions (Hyp):

$$A_{ij}(P_c,R_c)=A\times Hyp[i+j,(P_c+R_c),s\,A,s]\times Hyp[i,P_c,(P_c+R_c),i+j] \quad (2)$$

$$Hyp(N,N_0,M,L)=\binom{N_0}{N}\binom{M-N_0}{L-N}\Big/\binom{M}{L} \quad (3)$$

and the number of conjugated P and R cells are obtained respectively as:

$$P_c=\frac{F\times K_P}{1+F\times K_P}\,P,\ R_c=\frac{F\times K_R}{1+F\times K_R}\,R \quad (4)$$

where K_P and K_R are the conjugation constants of P and R cells with the APC respectively; and F is the total number of free APC sites, that is obtained by numerically solving the following equation:

$$F=s\times A-\frac{F\times K_P}{1+F\times K_P}P-\frac{F\times K_R}{1+F\times K_R}P \quad (5)$$

Note that, in order to obtain Eq. (4) and Eq. (5), the T-cell/APC-site conjugation and de-conjugation processes are assumed to be fast compared to cell proliferation, differentiation and death. This allows taking a quasi-steady state approximation for those quantities.

The behavior of this model can be best described in terms of two composite parameters G_R and G_P [36], which are defined by: $G_R=K_R\times\mu\times A/d$ and $G_P=K_P\times\pi\times A/d$, and represent respectively the growth indexes of R and P cells in the system.

Appendix B. Increasing the number of APCs according to a logistic growth kinetics

In some simulations (see text) the number of APCs is changed over time according to a logistic growth kinetics given by the formula:

$$A(t)=\frac{A_0\times A_m}{A_0+(A_m-A_0)\,e^{-v\times A_m\times t}} \quad (6)$$

Where:

A_0 The initial number of APCs
A_m The maximal value attained by the number of APC
v The kinetics constant, controlling the velocity of the increment in the APCs number

Nevertheless the results reported in this paper are qualitatively independent of the particular equation describing the growth kinetics of the APCs (data not shown). They only depend on the rate of growing of the APCs numbers as discussed on Fig. 3.

Appendix C. Modeling the effect of common infections on T cell mediated tolerance

There are two non-mutually exclusive scenarios by which common infections could affect the parameters in the model of T cell mediated tolerance described in Appendix A:

(A) According to the first scenario the average number of APCs, A, in each individual would be proportional to I, the incidence of infections in the population:

$$A=A_0+a\times I$$

where A_0 is the basal, genetically determined number of APCs and a is a proportionality constant.

To understand the effect of this postulated relationship on the model behavior we substitute A in the definitions of G_P and G_R given in Appendix A. This results in the following dependencies of G_P and G_R on the value of I:

$$G_P=K_P\times\pi\times A_0/d+(K_P\times\pi/d)\times a\times I$$

$$G_R=K_R\times\mu\times A_0/d+(K_R\times\mu/d)\times a\times I$$

Combining these relations to eliminate I we get the following relationship between G_P and G_R:

$$G_P=(K_P\times\pi/K_R\times\mu)\times G=(G^0_P/G^0_R)\times G$$

This equation shows that in this scenario, for any value of I, the point representing an individual in the parameter's space (G_R, G_P) always lies in a straight line that intercepts the zero point and the individual's basal position (G^0_R, G^0_P), i.e., for I=0.

(B) According to the second scenario, during responses to common infections there is some bystander stimulation of the growth of autoreactive regulatory and proinflammatory cell populations. To keep it simple, we assume that this bystander stimulation leads in each individual to an increase of the basal average growth rates of P and R cells that is proportional to I:

$$\pi=\pi_0\times(1+\beta_P\times I)$$

and

$$\mu=\mu_0\times(1+\beta_R\times I)$$

where π_0 and μ_0 are the basal, genetically determined proliferation rates of P and R, respectively (or the proliferation rate of P cells and the differentiation rate of R cells; both ways give equivalent results) and β_P and β_R are the respective proportionality constants.

As in the previous case, to understand the effect of these relationships on the model behavior we substitute them in the definitions of G_P and G_R. This results in the following dependencies of G_P and G_R on the value of I:

$$G_P=K_P\times\pi_0\times A/d+(K_P\times\pi_0\times A/d)\times\beta_P\times I$$

$$G_R=K_R\times\mu_0\times A/d+(K_R\times\mu_0\times A/d)\times\beta_R\times I$$

Combining these relations to eliminate I we get the following relationship between G_P and G_R:

$$G_P=G_P^0\times(1-\beta_P/\beta_R)+(G_P^0/G_R^0)\times(\beta_P/\beta_R)\times G_R$$

This equation shows that in this scenario, for any value of I, the point representing an individual in the parameter's space (G_R, G_P) lies in the straight line that intercepts is basal value ($G^0{}_R$, $G^0{}_P$) and has slope given by ($G^0{}_P$, $G^0{}_R$)$\times(\beta_P/\beta_R)$.

Finally, in both scenarios the tolerant or autoimmune-prone status of individuals being exposed to a given environmental level of infection is recorded according to the region, within the (G_R, G_P) parameter's space, in which their characterizing points are located.

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