Prof. Mawieh Hamad
School of Medicine
Taif University
TAIF Saudi Arabia

Articles

Mawieh Hamad and Ali Elkarmi

Modeling Acquired Immunity as an Outcome of the Interaction between Host-related Factors and Potential Antigen Repertoires

Key Words. Compartmental model, antigen repertoire; host-related factors, acquired immunity, self nonself discrimination; antigen receptor diversity; immunologic memory.

Abstract. *In an attempt to understand why different organisms defend against potential antigens differently, the influence of possible interactions between host-related factors and respective antigen repertoires on the complexity of host defense mechanisms was investigated. A compartmental model coupling these two variables was developed and tested. Data analysis suggests that the more complex the organism, the larger the size of its antigen repertoire. The two variables seem to advance in a parallel fashion suggesting that they could reach a state of equilibrium. Therefore, host-related factors may play a role in determining the size of the antigen repertoire on the one hand; on the other hand, increased antigen repertoire size may dictate the evolution of more complex mechanisms of immunity. Although the interplay between the two variables maintains some common themes in different groups of organisms, it results in clear differences pertinent to immunologic specificity, diversity, memory and self nonself discrimination.*

Rivista di Biologia / Biology Forum 99 (2006), pp. 429-444.

RB 99 (2006), pp. 429-444 = pp. 16 = 8 x 2

I Revisione: Autore 04.01.2007 Restituzione:

1. INTRODUCTION

Elaborate and sophisticated mechanisms of immunity have evolved in various groups of organisms over time (Du Pasquier [1989]). These mechanisms vary in complexity from one group of organisms to another. Although immunity is conferred by innate as well as acquired components, differences in the acquired arm of the immune system seem to be the major subject of variation. Differences in the degree to which acquired immunity in different groups of organism exhibit antigen specificity, antigen receptor diversity and the kind of mechanisms that generate it, immunologic memory, localization of the immune response and self nonself discrimination are well recognized (Hamad [2005]; Zapata [1983]; Du Pasquier [1976]; Kolb [1977]; Miller *et al.* [1986]; Kelsoe and Schulze [1987]). Why is it that different groups of organisms differ in the way in which they defend against foreign antigens? The relationship between host complexity and the complexity of the immune system of the host is well established (Du Pasquier [1989]; Kelsoe and Schulze [1987]; Awaya [1986]). Furthermore, it is logical to assume that as the size of the antigen repertoire increases, so does the complexity of host immune system. The question then is, could complex interactions between these two variables have any bearing on the complexity of the immune system as a whole? In other words, can evolutionary tailoring of host defense mechanisms compatible with the defense needs of the host be viewed as an outcome of such possible interactions? To approach this issue, the influence of host complexity or host-related factors on the size of the host-specific antigen repertoire and that of the size of antigen repertoire on the complexity of the host was theoretically investigated. A compartmental model accounting for possible interactions between these two variables was developed and tested.

2. METHODS

Model Formulation

The complexity of the immune system is assumed to be a func-

tion of the interaction between host-related factors (HRF) and antigen repertoires (AR). HRF pertains to aspects of the host like the degree of mobility, the degree of complexity of internal transport systems, the degree of interaction with the external environment and the degree of molecular complexity. AR is meant to describe the total number of antigens to which the host is potentially susceptible and hence may have specific receptors against. The model proposed to describe this interaction consists of two compartments (Figure 1). The interaction between these two compartments occurs such that the complexity of HRF influences the size of antigen repertoire and the size of the antigen repertoire influences the complexity of HRF and hence that of the immune system. The degree to which the two compartments influence one another is determined by two coefficients K12 and K21 as shown in figure 1. A biological system is said to be compartmental when its component entities can be grouped into a finite number of homogenous components. Assuming that the principle of superposition applies, then the compartmental system is first order. If we suppose that the antigens are introduced in compartment AR at a constant rate (zero order), and further suppose that rapid mixing occurs, then the exchange between the two compartments is first order. The amount of antigen in compartment AR will increase until it reaches an asymptotic value. Moreover, whatever the rate of introduction, as long as it remains within linearity, the kinetics of the system is controlled by K12, the constant exits from the compartment. Besides, there is no evidence in the literature to suggest otherwise. There is a constant input to the AR compartment represented by I where new antigens are added to the repertoire through genetic alterations and evolution. The appearance of new antigenic epitopes as a result of sequence-based mutations may serve as a good example in this case. I is a process of zero order. K20 coefficient represents the elimination of antigens that can no longer affect the host; K20 in this case is not a constant but rather a function of the HRF compartment; K20 follows a kinetic of the first order. The output is made out of compartment HRF to indicate that the process is close to neutralization, where the antigen no longer poses a threat to the host and the host has no specific receptors to interact with the antigen.

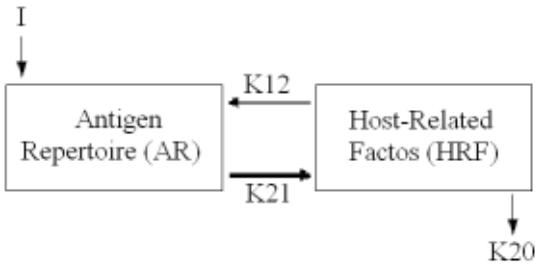

Fig. 1 – Compartmental model of the complexity of the immune system as a function of the interaction between host-related factors (HRF) and the antigen repertoire (AR).

Model Assumptions

The following assumptions were made: (i) the complexity of the immune system can be modeled as a linear compartmental system. (ii) This complexity can be modeled as two open compartments with a constant rate of input. (iii) The interaction between HRF and AR can be represented by first order differential equations. (iv) These first order differential equations represent the change in time that occurs in each compartment. (v) The initial values at time (t = 0) is such that there is no value for HRF and AR. In other words, at time 0 there are no antigen repertoires and no host-related factors. (vi) The process of elimination of certain antigens from antigen repertoires is assumed to be host-related.

Model Analysis

The two first order differential equations are:

$$dAR / dt = - K_{12}AR + K_{21}HRF + I$$
$$dHRF / dt = K_{21}\ AR - (K_{21} + K_{20})HRF$$
$$\text{Let } (K_{21} + K_{20}) = K_2$$

With the condition AR = HRF = 0 at time 0 and using Laplace transforms (hrf) and (ar) for HRF and AR, the preceding system becomes:

$$(S + K_{12})AR - K_{21}HRF = I / S =$$
$$- K_{12}AR + (S + K_2)HRF = 0$$

Thus:

$$\Delta = \begin{vmatrix} (S + K_{12}) & -K_{21}S \\ -K_{12} & (S + K_2) \end{vmatrix} \quad S(S + K_{12})(S + K_2) - K_{21}SK_{12} = S(S + a)(S + b)$$

Where -a and -b are the roots of the equation = 0 which can be shown to have only real roots. Thus,

$$AR / I = S + K_2 / S(S + a)(S + b)$$
$$HRF / I = K_{12} / S(S + a)(S + b)$$

Therefore, the antitransforms of the above equations give the following final solutions

$$AR / I = (K_2 / ab) + [(1 - K_2 / a) / (b - a)]e^{-at} - [(1 - K_2 / b) / (b - a)]e^{-bt}$$
$$HRF / I = (K_{12} / ab) - [K_{12} / a(b - a)]e^{-at} + [K_{12} / b(b - a)]e^{-bt}$$

In the case where continuous input to the system stops at time θ, that is t > θ, and the input behaves as a step function of I height starting at time t = 0 and ending at time t = θ, the final solution is:

$$AR / I = -[(1 - K_2/a) / (b - a)]e^{-a(t - \theta)} (1 - e^{-a\theta}) + [(1 - K2 / b) / (b - a)]e^{-b(t - \theta)} (1 - e^{-b\theta})$$
$$HRF / I = [K_{12} / a(b - a)]e^{-a(t - \theta)} (1 - e^{-a\theta}) - k_{12} / b(b - a)e^{-b(t - \theta)} (1 - e^{-b\theta})$$

For t = θ, the solution of the continuous input applies, and for the case of large θ; i.e, the equations have reached equilibrium, the step function case will correspond to the continuous input case without constant terms and with the sign changed.

3. RESULTS

The complexity of the immune system as a function of the in-

teraction between host-related factors and size of the antigen repertoire was modeled as a compartmental model as shown in figure 1. Model analysis suggests that the relationship between the two compartments is positive in nature. In other words, any increase in either variable is matched by a quantifiable increase in the other. To demonstrate the behavior of the two compartments of the model in the absence of actual data, two case scenarios are assumed. In the first case, it is assumed that the values of K12 and K21 = 0.2 whereas the value of K20 = 0.3 and I = 1.

Therefore,

$$AR = 8.33 - 0.334\, e^{-0.6t} + 8\, e^{-0.1t}$$
$$HRF = 3.33 + 0.67\, e^{-0.6t} - 4\, e^{-0.1t}$$

In the second case, it is assumed that K12 = K21 = 0.4, K20 = 0.6 and I = 1.

Therefore,

$$AR = 4.167 - 0.167\, e^{-1.2t} - 4\, e^{-0.2t}$$
$$HRF = 1.667 + 0.333\, e^{-1.2t} - 2\, e^{-0.2t}$$

The first case scenario with low coefficient values or slow exchange between the compartments gave a higher steady state values (8.33 and 3.33 for AR and HRF respectively). The second case scenario with high coefficient values or faster exchange between the compartments, gave a lower steady state values (4.167 and 1.667 for AR and HRF respectively). Therefore, the model predicts that there is an inverse relationship between the values of the coefficients K12 and K21 which express the rate of exchange between the two compartments and the steady state (plateau) value reached at $t = \infty$. In other words, the higher the value of coefficients the lower the complexity of host related factors (part of which is the immune system) and the lower the antigen repertoire.

Based on these finding, the first case scenario was used to illustrate the behavior of a mammalian immune system as an example of high complexity (Figure 2a). The second case scenario was used to illustrate the behavior of a plant immune system as an example of "relatively" low complexity (Figure 2b). This suggests that both

compartments can potentially reach a state of equilibrium and plateau following a long period of interaction. In other words:

$$\lim_{t \to \infty} AR(t) = K_2 / ab$$

$$\lim_{t \to \infty} HRF(t) = K_{12} / ab$$

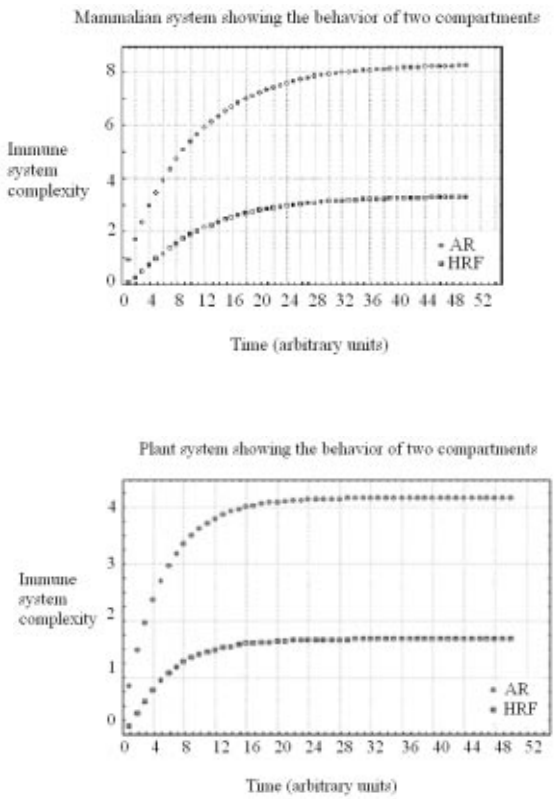

Figure 2 –The behavior of the AR and HRF compartments in (a) a mammalian immune system and (b) a plant immune system based on assumed values. X-axis represents time in arbitrary units and Y-axis represents overall immune system complexity. The degree of complexity was assigned arbitrary numbers for illustration purposes.

The influence of various host-related structural, behavioral and physiologic factors (HRF) as well as molecular complexity on the size of host-specific antigen repertoire (AR) is depicted in figure 3, which suggests that increased host complexity results in increased host susceptibility to new antigens. This could be achieved by the appearance of new molecules for anchoring or interacting with antigens, enhanced deposition and distribution mechanisms as well as the exposure to wider pools of antigens among many other mechanisms. Exact contributions of single components of host complexity on the size of the antigen repertoire are not discussed. Furthermore, the arrangement of the single components bears no significance evolutionary or otherwise. The list of host-related factors depicted in the figure is not exhaustive; additional factors may play a role in this context.

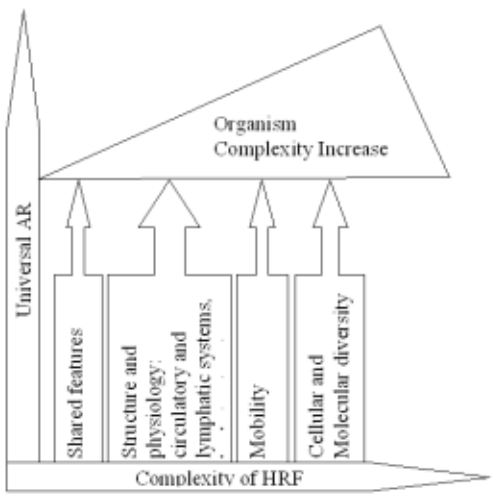

Figure 3 – The influence of various host-related factors on the size of host-specific antigen repertoires.

Candidate aspects of immunity or host resistance influenced by the size of the antigen repertoire are shown in figure 4. As shown in the figure, increased size of the antigen repertoire results in the appearance of more complex and sophisticated mechanisms of

immunity. Antigen receptor diversity and the mechanisms that generate it, the shift from localized to systemic responses in addition to the evolution of specific memory are considered. Additionally, only aspects of the acquired immune system are considered in terms of the influence of the size of host-specific antigen repertoire. Neither the scale nor the position of the various components in the diagram is of any significance.

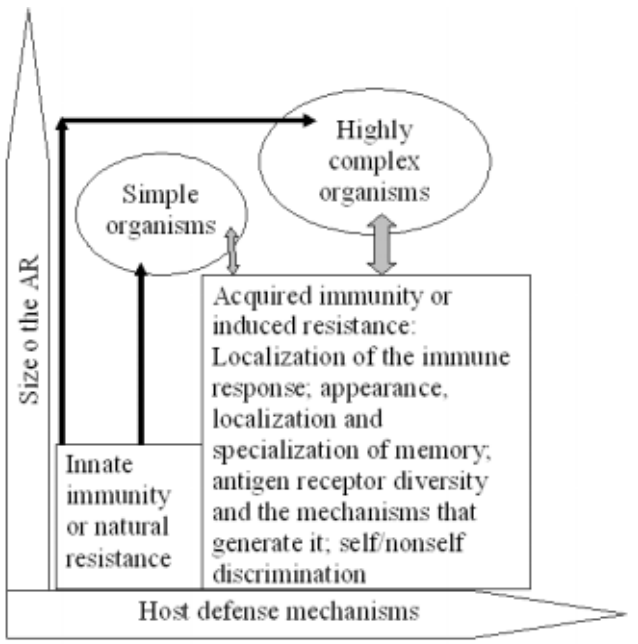

Figure 4 – Aspects of acquired immunity or host resistance that may be potentially influenced by the size of the antigen repertoire.

4. DISCUSSION

The compartmental model developed in this study suggests that: (i) increased host complexity is associated with an increase in the size of host-specific antigen repertoire. (ii) Increased complexity in these two compartments results in increased complexity in host defense mechanisms. (iii) Complexity in both compartments

reaches a state of equilibrium after a time period of an evolutionary scale. To discuss the model in practical terms, comparative analysis of acquired immunity in mammals and induced host resistance in plants was presented in the results. These two groups were chosen as they are very distinct and because acquired defense mechanisms have been studied in some detail in representative members from both groups. Innate immunity was not considered in the discussion as innate immunity has come to be part of immunity only by default. This, not withstanding the fact that recent studies have demonstrated that several components of the innate immune system use sophisticated mechanisms of antigen recognition (Medzhitov and Janeway [1997], [1998]; Imler and Hoffmann [2000]). In fact, several similar mechanisms of innate immunity are operative in plants and higher animals (Medzhitov and Janeway [1998]; Borregaard *et al.* [2000]).

Mammals are mobile while plants are not, which hints to the possibility that the diversity of the potential antigen repertoire that could be encountered by mammals is far greater than that in the case of plants (Lippincott and Lippincott [1984]). The mode of nutrition and respiration in mammals allows for entry of very large numbers of different antigens through food, water and air. Mammals have digestive, respiratory, reproductive and excretory systems with openings to the outside linking the internal environment of the organism with its external environment. Furthermore, mammalian cells and tissues are connected together through circulatory and lymphatic systems which help in effective distribution and dissemination of antigens to various organs and tissues of the body. Accordingly, the likelihood of direct and indirect contacts between mammalian tissues and cells and the outside environment with its massive repertoire of antigens is greatly increased. Mammalian-like digestive, respiratory, reproductive, excretory, circulatory and lymphatic systems are lacking in plants. In fact, the majority of antigens gain entry into plants through localized natural openings like stomata and lenticels (Royle [1976]; Billing [1987]). Additionally, the cell wall restricts infection in plant cells except in cases where cell wall antigen-specific receptors representing points of entry for tropic pathogens are present or in cases where the cell wall is breached (Royle [1976]; Cooper [1981]). Mammalian cells

lack cell walls resulting in less restriction on cell-pathogen interactions. The diversity of mammalian cells and molecules is far greater than that in plants due to many factors like, for example, the mode of reproduction (Roberts and Boothroyd [1972]).

Increased diversity of cell types could potentially result in increased diversity of cell surface moieties and therefore increased range of tissue tropism for a wider range of pathogens. Collectively, host-related factors and attributes are likely to have significant additive effect on the size of host-specific antigen repertoires (Figure 3). As the organism becomes more susceptible to a greater number of antigens, the evolution of more complex mechanisms of defense ensues. Innate immunity or natural resistance, which implies the prevention of invasion rather than the recognition and elimination of antigens, has evolved as a host defense mechanism by default. As such, it is unlikely that antigen repertoires have any influence on the development or evolution of innate immunity (Borregaard *et al.* [2000]) (Figure 4). It is likely however that acquired immunity or induced resistance has gradually evolved as evolutionary adaptations to protect the respective host against all potential antigens. Differences between acquired immunity in mammals and induced resistance in plants are discernable (Billing [1987]; Staskawicz *et al.* [1995]; Gianinazzi [1984]). Of interest here are issues pertaining to immunologic specificity, antigen receptor diversity and how it is generated, immunologic memory and self nonself discrimination.

Mammalian acquired immunity is systemic in nature occurring in the form of specialized cells that can be mobilized to different parts of the body. These cells express a diverse repertoire of antigen receptors generated through complex molecular mechanisms. As part of the acquired immune response, specific memory T and B lymphocytes form following primary encounter between the immune system and the antigen to ensure stronger long-term immunity against future attacks by the same antigen. Mammalian immune systems distinguish between self and nonself via expressing the major histocompatibility complex (MHC) family of molecules to carry out its normal functions without causing autoimmunity to the host.

Plant resistance to a specific pathogen occurs if the plant has a

resistance gene (R) whose product interacts with the products of an avirulence gene (avr) in the pathogen (Roberts and Boothroyd [1972]; Gianinazzi [1984]; Moffat [1994]; Bent *et al.* [1994]). Such interactions initiate the "well known" hypersensitivity reaction that results in the release of chemicals (Roberts and Boothroyd [1972]; Gianinazzi [1984]; Ovreem [1976]) to stop the spread of the pathogen. Mutations in R or avr genes lead to compatible interactions that result in host susceptibility. Plant R genes represent antigen receptors at the genetic level; both qualitative and quantitative diversity of R genes in a specific plant species is essential to account for all potential pathogens if they are to be eliminated in this fashion. However, the number of resistance genes that may exist in any plant is limited (Innes [1995]) even if the gene-for-gene hypothesis (Flor [1946]) is modified to a genes-for-gene or genes-for-genes version (Innes [1995]). This although many plant species are resistant to the majority of existing pathogens; how to reconcile these contradictions? It is possible that the diversity of plant antigen repertoires is limited and hence generation of diverse repertoires of antigen receptors is useless. It follows that plants need not express specific receptors against potential-less antigens. Interestingly, many plant species are resistant to a wide range of pathogens merely by the absence of pathogen-specific receptors to such pathogens (Staskawicz *et al.* [1995]; Ovreem [1976]).

Generation of memory has been documented in many plants (Ryan [1984]; Fletcher [1975]; Bennet [1951]; Bar-Joseph [1978]). Plant immune responses mostly occur at the cell and tissue levels perhaps either because various parts of a plant are subject to different classes of antigens or perhaps due to the lack of means to transport such responses or a combination of both. As an extension of the immune response, memory is therefore expected to be local in plants. Additionally, where localization of memory limits its value in mammals, it seems appropriate in plants. The general nature of immunologic memory in plants (Fletcher [1975]; Bennet [1951]; Bar-Joseph [1978]) can be explained by the possibility that the size of antigen repertoire is so limited that very similar responses are mounted against all potential antigens. The capacity to discriminate between self and nonself in plants is difficult to discern, however plant grafts show a pattern of success or

failure similar to organ transplantation in mammals (Tinley-Basset [1984]; Neilson-Jones [1969]). Is it possible that plants express MHC-like molecules that enable the plant to see self or nonself? more fundamentally, do plants need to express MHC-like molecules? Taking into consideration the possibility that the diversity of potential plant antigens is limited, the diversity of plant antigen receptors is limited and the fact that no stochastic mechanisms are involved in generating plant antigen receptor diversity, plants may not have to distinguish between self and nonself to begin with.

5. CONCLUSIONS

It is clear that interactions between host-related factors and respective antigen repertoires seem to actively participate in the shaping of acquired immunity. This finding however raises more questions than answers. Of relevance are questions pertinent to the nature and time scale of such interactions, the means of defining host complexity in quantifiable terms and the mechanisms by which such interactions influence the respective variable. Nonetheless, the model shows that the immune system, like other aspects of living matter, is dynamic and subject to manipulation by forces other than its own. It evolves with time as a result of evolutionary forces like the antigen repertoire size and host complexity. Results presented in this study should facilitate the characterization of common themes among the immune systems of various groups of organisms.

M. Hamad, Taif University School of Medicine, Saudi Arabia
A. Elkarmi, Department of Biology & Biotechnology, Hashemite University, Jordan

REFERENCES

Awaya, K. [1986], A Study on the Phylogeny of the Immune System. *As. Med. J.* **29**: 191-201.

Bar-Joseph, M. [1978], Cross Protection Incompleteness: A Possible Cause for Natural Spread of *citrus tristeza* Virus after a Prolonged Lag Period in Israel. *Phytopathology* **68**: 1110-1111.

Bent, A.F., B.N. Kunkel, D. Dahlbeck, K.L. Brown, R. Schmidt, J., Giraudat, J.

Leung and B.J. Staskawicz [1994], RPS2 of *Arabidopsis thaliana*: A Leucinerich Repeat Class of Plant Disease Resistance Genes. *Science* **265**: 1856-1860.

Bennet, C.W. [1951], Interference Phenomena between Plant Viruses. *Ann. Rev. Microbiol.* **5**: 295-308.

Billing, E. [1987], *Bacteria as Plant Pathogens*. Van Nostrand Reinhold, London, UK.

Borregaard, N., T. Elsbach, P. Garred and A. Svejgaard [2000], Innate Immunity: from Plants to Man. *Immunol. Today* **21**(2): 68-70.

Cooper, R.M. [1981], Pathogen-induced Changes in Host Ultrastructure. In R.C. Staples and G.H. Toenniessen (eds.), *Plant Disease Control,* John Wiley and Sons, New York, pp. 105-138.

Du Pasquier, L. [1976], Phylogenies of the Vertebrate Immune System. In F. Melchers and K. Rajewsky (eds.), *Mosbacher Colloquium 27,* Springer, Berlin, pp. 1-115.

Du Pasquier, L. [1989], Evolution of the Immune System. In W. Paul (ed.), *Fundamental Immunology,* Raven Press, New York, pp. 139-165.

Fletcher, J.T. [1975], The Use of Avirulent Virus Strains to Protect Plants Against the Effects of Virulent Strains. *Ann. Appl. Biol.* **89**: 110-114.

Flor, H.H. [1946], Genetics of Pathogenicity in *Melamspora lini. J. Agr. Res.* **73**: 335-357.

Gianinazzi, S. [1984], Genetic and Molecular Aspects of Resistance Induced by Infections or Chemicals. In T. Kosuge, E.W. Nester (eds.), *Plant-Microbe Interactions,* Macmillan Publishing Company, New York, pp. 321-340.

Hamad, M. [2005], Plant Resistance versus Animal Immunity: The Faithful Divorce. *Rivista di Biologia/Biology Forum* **98:** 371-392.

Imler, J.L and J.A. Hoffman [2000], Signaling Mechanisms in the Antimicrobial Host Defense of Drosophila. *Curr. Opin. Microbiol.* **3**: 16-22.

Innes, R.W. [1995]. Plant-parasite Interactions: Has the Gene-for-gene Model Become Outdated? *Trends in Microbiology* **3**: 483-485.

Kelsoe, G. and D.H. Schulze [1987], *Evolution and Vertebrate Immunity: The Antigen Receptor and MHC Gene Families*. University of Texas Press, Austin.

Kolb, H. [1977], On the Phylogenetic Origin of the Immune System: A Hypothesis. *Dev. Comp. Immunol.* **1**: 193-206.

Lippincott, J.A. and B.B. Lippincott [1984], Concepts and Experimental Approaches in Host-microbe Interactions. In T. Kosuge, E.W. Nester (eds.), *Plant-Microbe Interactions*, Macmillan Publishing Company, New York, pp. 195-210.

Medzhitov, R. and C. Janeway [1997], Innate Immunity: The Virtues of a Nonclonal System of Recognition. *Cell* **91**: 295-298.

Medzhitov, R. and C. Janeway [1998], Self-defense: The Fruit Fly System. *Proc. Natl. Acad. Sci. USA* **95**: 429-430.

Miller, N.W., A. Deuter and L.W. Clem [1986], Phylogeny of Lymphocyte Heterogeneity: The Cellular Requirements of the Mixed Leukocyte Reaction with Channel Catfish. *Immunol*ogy **59**: 123-128.

Moffat, S. [1994], Mapping the Sequence of Disease Resistance. *Science* **265**: 1804-1805.

Neilson-Jones, W. [1969], Plant Chimeras. In K. Mellanby (ed.), *Methuen's Monographs on Biological Subjects,* The Camelot Press, London, pp. 1-15.

Roberts, A.D. and C.W. Boothroyd [1972], *Fundamentals of Plant Pathology,* W.H. Freeman and Company, San Francisco, USA.
Royle, D.J. [1976], Structural Features of Resistance in Plants. In J. Friend and D.R. Threfall (eds.), *Biochemical Aspects of Plant-Parasite Relationships,* Academic Press, New York, pp. 62-193.
Ryan, C.A. [1984], Systemic Responses to Wounding. In T. Kosuge, E.W. Nester (eds.), *Plant-Microbe Interactions,* Macmillan Publishing Company, New York, pp. 307-320.
Ovreem, J.C. [1976], Pre-existing Antimicrobial Substances in Plants and their Role in Disease Resistance. In J. Friend and D.R. Threfall (eds.), *Biochemical Aspects of Plant-Parasite Relationships,* Academic Press, New York, pp. 195-207.
Staskawicz, B.J., F.M. Ausbel, B.J. Baker, J.G. Ellis and J.D.G. Jones. [1995], Molecular Genetics of Plant Disease Resistance. *Science* **2**68: 661-667.
Tinley-Bassett, R.A.E. [1984], *Plant Chimeras*. Edward Arnold, London, UK.
Zapata, A. [1983], Phylogeny of the Fish Immune System. *Bull. Inst. Pasteur* **81**: 165-186.

Mawieh Hamad e Ali Elkarmi

MODELLIZZAZIONE DELL'IMMUNITÀ ACQUISITA COME RISULTATO DELL'INTERAZIONE TRA FATTORI LEGATI ALL'OSPITE E REPERTORI ANTIGENICI POTENZIALI

Riassunto

È stata studiata la possibilità che esista una relazione tra complessità di un organismo e dimensione del suo repertorio antigenico. A questo scopo è stato sviluppato e testato un modello che accoppia queste due variabili. L'analisi dei dati suggerisce che più un organismo è complesso, maggiore è la dimensione del suo repertorio antigenico. Le due variabili sembrano avanzare in modo parallelo suggerendo la possibilità che raggiungano uno stato di equilibrio. Dunque, mentre da un lato i fattori legati all'ospite eserciterebbero un'influenza sulla dimensione del repertorio antigenico, dall'altro un aumento della dimensione del repertorio antigenico potrebbe innescare l'evoluzione di meccanismi immunitari più complessi.