Chronic antigenic stress, immunosenescence and human survivorship over the 3 last centuries: heuristic value of a mathematical model

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Abstract

In previous investigations we pursued the hypothesis that lifelong, chronic antigenic load (CAL) is the major driving force of immunosenescence, which impacts on human lifespan by reducing the number of virgin antigen-non experienced (ANE) T cells, and filling the immunological space with expanded clones of memory and effector, antigen-experienced (AE) T cells. A model has been proposed to relate CAL with the conversion rate from ANE to AE CD8+ T cells. In addition, in order to account for individual variations of immunosenescence and lifespan, a noise term has been introduced to describe the individual fluctuations of CAL. This model was able to follow with a reasonable approximation the age-related decrease of ANE CD8+ T cells, as well as human survival curves.

In this paper we extend this approach to historical survival curves, starting from 1750 until present days, and show that the quality of the fit of historical demographic data improves as we approach the recent, quantitative and qualitative decrease of CAL. Indeed, the almost linearity in the increase of lifespan and in the decrease of the noise fluctuation amplitude within this historical period suggests that the improvement of life conditions has steadily lowered the intensity of CAL and restricted the variability which results from the interaction between the individuals and their immunological environment. On the whole, this approach allows to appreciate when and how immunosenescence has started to impact on survivorship, and predicts its increasing, crucial role in explaining human mortality in hygienized, economically developed societies.

Keywords: Immunosenescence; Antigenic stress; Virgin T cells; Human mortality; Immune system model; Stochastic processes.

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1. Introduction

Recent data suggest that age-associated immune remodelling, i.e. immunosenescence, may have a clinical impact, being responsible, at least in part, of some major age-related pathologies. However, until now, no reliable biomarker of immunosenescence is available. Taking into account that a major characteristic of immunosenescence is the accumulation of memory plus effector antigen-experienced (AE) T cells (Fagnoni et al., 1996; Wack et al., 1998), accompanied by a decrease of virgin antigen-non experienced (ANE) T cells (Fagnoni et al., 2000), it is reasonable to hypothesize that such parameters can be assumed bonafide as candidate biomarkers of immunosenescence (Franceschi et al., 1999; Franceschi et al., 2000a; Pawelec et al., 2002a). Indeed, the so called ”Immunological Risk Phenotype”, capable of predicting impinging morbidity and mortality in the elderly, includes the number of CD4+ and CD8+ AE T cells, as well as other parameters related to chronic inflammation (Franceschi et al., 2000c; Bonafe et al., 2001; Pawelec et al., 2002b). A unifying approach suggests that both the accumulation and the expansion of AE T cells, and particulary of CD8+ T cells, and the increase of inflammatory markers present in old people, is a consequence of the largely inescapable, lifelong chronic antigenic load (CAL) (Franceschi et al., 2000b; Franceschi et al., 2000c). This scenario has been conceptualized and modeled, and the results suggest that the number and the concentration of ANE CD95- CD8+ T cells (Fagnoni et al., 2000) can be assumed as a biomarker capable of predicting mortality in humans (Luciani et al., 2001a; Luciani et al., 2001b). In this model we pursued the hypothesis that CAL can be represented by an average component which quantifies the conversion rate from ANE CD95- to AE CD95+ CD8+ T cells and determines the average lifespan. In addition, in order to account for individual variations of immunosenescence and lifespan, we introduced an additional noise term for the fluctuations of CAL. This parameter was able to describe with a reasonable approximation not only the age-related decrease of AE CD8+ T cells but also the shape of human survival curves.

In the present paper we extend this model to human survival curves starting from 1750 until present days in Swedish cohorts, and show that the fitting of these demographic data improves as we approach recent, improved conditions of life, where CAL underwent a qualitative and quantitative reduction, suggesting that immunosenescence is becoming more and more important as a possible cause of mortality.

2. Stochastic model for virgin CD8+ T lymphocytes

In order to describe the CD8+ T lymphocyte dynamics on a long time scale, we consider the relation between the ANE CD95- and AE CD95+ CD8+ T cell pools. Indeed, the model we have recently proposed (Luciani et al., 2001a; Luciani et al., 2001b; Mariani et al., 2002), takes into account the conversion from ANE CD95- (V) to AE CD95+ (M)
CD8+ T cells occurring with a constant rate $\alpha$ due to primary antigenic stimulation. The secondary antigenic stimulation is responsible for a further expansion of the $M$ pool with a constant rate $\beta$, which causes an additional reduction of the $V$ pool due to the conservation of the overall $T$ cell compartment

$$V(t) + M(t) = V_0$$

for initial (at birth) conditions $V(0) = V_0$ and $M(0) = 0$. The evolution equations for our system read

$$\frac{dV}{dt} = -\alpha V(t) - \beta M(t)$$

$$\frac{dM}{dt} = \alpha V(t) + \beta M(t)$$

and we note that, being $V + M$ constant in our approximation, also their concentrations satisfy the same equations 2 and 3. The parameters $\alpha$ and $\beta$ average the interaction between genetics and CAL (assumed to be almost constant during lifespan), while the individual immunological histories are described by introducing a fluctuating term $\xi(t)$ in our equations. We assume that, for each individual, $V$ and $M$ represent the number of Virgin and Memory+Effector lymphocytes until the time $T$, when $V(T) = 0$, which is assumed to be the death age of the individual. The negative solutions, for $t > T$, have no immunological meaning, even though they are mathematically defined. Assuming a white noise approximation for the fluctuations, the equation for the ANE T cell concentration $v = V/(V + M)$ reads

$$\frac{dv}{dt} = -(\alpha - \beta) v(t) - \beta + \epsilon \xi(t)$$

Since the white noise has zero average, the mean solution is given by

$$\langle v(t) \rangle = \frac{\alpha e^{-t(\alpha-\beta)} - \beta}{\alpha - \beta}$$

the probability density function is Gaussian, and the variance around the mean value is given by

$$\sigma^2(t) = \frac{\epsilon^2}{2\alpha} (1 - e^{-2\alpha t})$$

so that $\sigma(t)$ vanishes at the origin like $\sqrt{t}$ and reaches a constant limit for $t \to \infty$ (left panel of figure 1). Some further details on the mathematical aspects of model (4) are given in Appendix I.
3. Survival probabilities

We assume the ANE CD95- CD8+ T cell concentration as a biomarker of mortality, which implies that an organism dies when this cell pool is exhausted (Fagnoi et al., 2000) and we identify the concentration of this T cell subset with a sort of vitality function, often proposed to relate individual heterogeneity to demographic survival probability (Yashin et al., 2000; Piantanelli et al., 2001; Rossolini et al., 2001). As a first consequence of this assumption, the average death age $T$ of the population depends on the time at which $\langle v \rangle(T) = 0$, whereas the variety of immunological histories, allowed by the presence of the noise term $\xi(t)$ in our equation, gives a spread of the individual lifespan and determines their survival probability function. The exact survival probability $S_{FP}(t)$ is obtained by progressively removing the individuals, whose ANE CD8+ T cell concentration reaches zero before time $t$ (first passage problem). A very close upper bound $S(t)$ to $S_{FP}(t)$ is obtained by counting as survivors all the individuals whose ANE CD8+ T cell concentration is positive at a time $t$, independently of values assumed at previous times (equation 7). With this procedure we count as survivors even those individuals whose ANE CD8+ T cell concentration has reached zero before time $t$, but comes back later to a positive value, owing to favorable fluctuations. However, due to the exponential decrease of $\langle v \rangle(t)$ these anomalous survivors occur with a very low probability and increase the survival of a
negligible amount. The numerical comparison, shown in Figure 1 (central panel), between the exact survival curve (lower line) and the survival curve deriving from the simplified procedure (upper line) confirms the validity of this approximation. Despite this inaccuracy, this procedure is convenient because of its very simple mathematical expression

\[
S(t) = \frac{1}{\sqrt{2\pi}} \int_{-\langle v \rangle(t)/\sigma(t)}^{+\infty} e^{-\frac{u^2}{2\sigma(t)^2}} du \equiv \frac{1}{2} \text{Erfc}\left(-\frac{\langle v \rangle(t)}{\sqrt{2}\sigma(t)}\right)
\]  

(7)

The left panel of Figure 1 shows a comparison of the experimental data of the ANE CD8+ T cell concentration with the average trajectory and the spread of two standard deviations around it. We observe that the corresponding mortality rate, shown in the right panel of Figure 1, starts with zero value and reaches a maximum slightly before twice the mean lifetime \(2T\), then lowering to zero with an asymptotic exponential decrease after the extreme limit of the human life. Indeed, a flattening in the increase of mortality rate with respect to the steady exponential growth of typical Gomperz law has been experimentally reported (Vaupel et al., 1998). See Appendix II.

4. Bestfitting of historical survival data

In order to infer the historical changes of parameters \(\alpha\), \(\beta\) and \(\epsilon\) of our model, we have compared the survival probability function \(S(t)\), given by equation (7), with the historical records of Swedish cohorts born in the period [1750−1910] (taken at regular time intervals of 20 years). These data were chosen owing to their availability and remarkable accuracy. The bestfitting between the function \(S(t)\) and the different sets of data, associates to every cohort specific values of the parameters \(\alpha\), \(\beta\) and \(\epsilon\). These values have to be interpreted as an average of the interaction between genetics and environmental CAL, calculated over the cohort during its lifespan. The individual immunological histories are described by the fluctuating term in our equations, whose amplitude is given by the parameter \(\epsilon\).

Our procedure corresponds to taking averages on an almost constant time window (\(\approx 100\) years), whose starting point varies regularly in order to grasp the slow variations of the process under investigation (immunosenescence). The final aim is to look at the time variation of the noise amplitude \(\epsilon\), obtained by fitting the demographic data, and to infer the evolution and the qualitative changes concerning the role of immunosenescence as mortality factor. Since our model describes the behaviour of the clonotipic immune system, the concentration of ANE CD8+ T cells appears to be a reliable biomarker of mortality, starting from mature age, identified as half the average lifespan \(T\), where \(S(T) = 1/2\). Taking into account this immunological assumption, we have built from each cohort the relative subcohort of the survivors at \(t = T/2\), and we have best-fitted the corresponding survival data with our survival probability function \(S(t)\). On an historical interval of few centuries, very short on a evolutionary time scale, we suppose that the average genetic property of a geographically determined population did not change appreciably. Hence, we can attribute any variation of the parameters on this interval to the changes of the environment, in this case identified with the burden of CAL.
Figure 2
Best fit of survival probability function $S(t)$ given by equation 7 (continuous line) to demographic survival data of Swedish subcohorts in the period [1750–1910]

$S(t)$ = human survival probability function for a specific cohort (the birth year is indicated at the top of each figure) depending on the age of individuals.

At first we impose that the historical data records of each subcohort fix the $T(\alpha, \beta)$ value as the age in which half the initial subcohort is dead. The two remaining free parameters, one of which is the noise amplitude $\epsilon$, are determined by minimizing the least square deviation between probability function and the data. The results of the best-fitting procedure is shown in Figure 2.

The left panel of F shows that the amplitude of the CAL fluctuation decreases almost linearly with time ($\epsilon(t) = 0.243 - 1.15 \times 10^{-4} \times t$), whereas the central panel shows that mean life time has a linear increase ($T(t) = -147 + 0.117t$). This implies a steady decrease
of the average CAL, on which \( T \) depends via the conversion coefficients \( \alpha \) and \( \beta \), as well as a steady decrease of the amplitude of its fluctuations with time. This result can be attributed to the improving of the standard of living, including hygienic conditions, health care and food quality.

The right panel of Figure 3 shows that the deviation from the demographic data, expressed by \( \chi^2 \), has a decreasing trend, excluding a short period in the middle of the XIX century. This analysis suggests that our model is best suited to interpret recent human survival data and the immunological characteristics of old people associated with mortality. This interpretation agrees with the fact that during the XX century physiological aging and immunosenescence fully emerged in developed countries by removing other premature causes of death. In other words, we can envisage that the improvement of environmental conditions and the progressive hygienization of the world in the last three centuries has been accompanied by a progressive decrease of the lifelong CAL, which promoted both an extension of lifespan (Oeppen et al., 2002) and the full expression of major characteristics of immunosenescence considered in our model, such as the accumulation of memory CD8+ T cells and the exhaustion of virgin CD8+ T cells (Fagnoni et al., 1996; Fagnoni et al., 2000). The fact that our model fits much better the survival data of more recent cohorts (Figure 2, Figure 3-right panel) suggests that the relationship between mortality and immunosenescence is becoming progressively more stringent and causally related (Franceschi et al., 1999; Franceschi et al., 2000a; Franceschi et al., 2000b).

**Figure 3**

Left panel: historical variation of the noise amplitude \( \epsilon \) (open circles) obtained by bestfit procedure and its linear approximation \((\epsilon(t)=0.243−1.15\times10^{-4} \cdot t)\); Center panel: historical variation of mean lifetime \( T \) (open circles) obtained by bestfit procedure and its linear approximation \((T(t)=−147+0.117 \cdot t)\); Right panel: mean square deviation \( \chi^2 = \sum_i (S(t_i)−S_{dem}(t_i))^2 \) obtained from the fits of the survival function \( S \) of our model to the demographic data of Swedish cohorts born in the period [1750,1910], shown in Figure 2.

\( \epsilon \) = value of the amplitude of noise in the bestfit curve of the immunologological model for each cohort over its birth year.

\( T \) = mean lifespan in years for each cohort over its birth year.

\( \chi^2 \) = value of the squared deviation between the bestfit curve given by our model and data for each cohort over its birth year.
A simplified two parameters model

We have also considered a simplified version of the model in which we impose the constraint $\alpha T = 1$ which is suggested by the fit of the immunological data of ANE CD8$^+$ concentrations which give $\alpha/\beta \simeq 3$. Imposing the constraint $\alpha/\beta = e$, we have $\alpha T = 1$ and the quality of the fit to the Swedish cohorts is slightly worse, but still comparable with the previous one. The noise amplitude still has an almost linear decrease though the initial value and the slope are smaller by 50% and the linear fit gives $\epsilon(t) = 0.143 - 6.35 \times 10^{-5} t$. In this case we obtain immediately $\alpha(t) = 1/T(t)$ and $\beta(t) = 1/(eT(t))$. For completeness we have analyzed the survival data of our cohorts with a two parameters model equivalent to the classical two parameters Gomperz law, $S = \exp(-CT(e^{t/T} - 1))$ obtained in a the framework of a stochastic approach to the theory of survival. The fitting quality, for the subcohorts of 5 years old survivors is comparable with the previous one (a peak of $\chi^2$ is still present in the second half of the XIX century). The amplitude of stochastic fluctuations $\epsilon$, still exhibits a decrease comparable with the previous one.

5. Conclusions

The immunological stochastic model we have used describes the time evolution for ANE CD8$^+$ T cell concentration during the human lifespan and, considering this cell concentration as a biomarker of mortality, gives a mathematical expression of the survival curve for adult age $t > T/2$ in good agreement with the demographic data.

The CAL explains the spread of ANE CD8$^+$ T cell concentration in a given population, and the flattening of the survival probability curves at very advanced ages. Within this scenario, a decrease of the fluctuation amplitude, namely of CAL intensity, implies a decrease of the spread of individual immunological histories around a mean value, and a related rectangularization of the survival probability curve, whereas a decrease of the average value of CAL corresponds to a decrease of the conversion rate from ANE to AE CD8$^+$ T cells, that leads to an increase of the average value of the lifespan.

The historical evolution of the CAL parameters, inferred from the demographic data relative to cohorts of humans born from 1750 to 1910, shows that a reshaping of the impact of CAL over the survival of the population occurred. The noise amplitude decreases linearly whereas lifetime increases linearly, corresponding to the constant improvement of the life standard during the last two and a half centuries.

Finally, the improvement of the fit quality between our model and the most recent demographic data suggests that a change in the causes of mortality, likely to be ascribed to an increasing role of CAL and inflamm-aging (Franceschi et al., 2000a), occurred concomitantly with the increasing lifespan of the population.

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References


**Appendix I**

The model (4) for the virgin CD8+ T cells concentration describes the effect of chronic antigenic stress as an additive white noise. This is the fluctuating part of the chronic stress, the average component being included in the coefficients $\alpha$ and $\beta$. This model is equivalent to previous one for the number of virgin(V) and memory plus effector(M) CD8+ T cells if we introduce a noise $\epsilon \xi(t)$ in equation (2) and the opposite term in equation (3) so that the total number $V + M$ is still conserved. One might object that from an immunological viewpoint this is not well justified. A model for the number $V_*$, $M_*$ of CD8+ T lymphocytes where $V_*$ satisfies equation (2) with an additive white noise $\epsilon \xi(t)$ and $M_*$ satisfies equation (3) is certainly more adequate since the fluctuations of the chronic stress mainly affect the virgin T cells pool and only in an indirect way the pool of memory plus effector T cells. The equation for the virgin T cells concentration $v_*(t) = V_*/(V_* + M_*)$ is different from (4) since in this case $V_*(t) + M_*(t)$ is no longer conserved. However it can be checked that the average values $\langle v_*(t) \rangle$ differs from $\langle v(t) \rangle$ only by a second order term in the noise amplitude $O(\epsilon^2)$ and the variances are asymptotically equal at the lowest order $\epsilon^2$. For the chosen values of the parameters the statistical results obtained from $v$ and $v_*$ are comparable, so that we refer to $v(t)$ which satisfies a simpler linear equation. The trajectory $v(t)$ of each individual describes the evolution of the virgin T cells concentration until $v(t_1) = 0$: at that instant the individual dies and we have to define $v(t) = 0$ for $t > t_1$ (first passage condition).

**Appendix II**

To compute the survival probability $S_{ex}(t)$ at time $t$ we count all the trajectories which
reach a positive value $v(t) > 0$. Obviously, all the trajectories which have previously reached the line $v = 0$ (dead people) are absent. This function can only be evaluated by a numerical procedure. However, we can provide an accurate analytical upper bound to it. To this end we extend the trajectories beyond the time at which they cross $v = 0$, as for the standard stochastic process. In this case, if we count all the trajectories which are positive at time $t$, we count also the ones which have assumed negative values before, and the corresponding estimate to the survival probability $S(t)$ is an upper bound to $S_{\text{ex}}(t)$. These trajectories, corresponding to resuscitated individuals, are a small number in the range of parameters $\alpha, \beta, \epsilon$, of immunological interest. As a consequence, this upper bound is also a good approximation to $S_{\text{ex}}(t)$ as shown by the middle frame of figure 2.