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Chronic Lymphocytic Leukemia, Advantages of Monoclones?

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Abstract

From a basic biological point of view, genetic traits from the human genome have been selected during a long evolution in the fight for fitness. Since the susceptibility for CLL has a genotype, a theoretical question about its advantage is relevant. This is a question about mutated monoclones and whether they are an advantage to man. We suggest that the genetic capability to provide such monoclones could be explained as reminiscence from the fetal life like a "Bad for the postnates, good for the prenates" principle. Some examples are described, e.g. the feto-maternal processing of endogenous retrovirus in the production of placenta-specific transcripts of several genes in a ceasefire balance with potential infectious exogenous retrovirus. The regulation of some cytokine reactions affected lymphocytes and monocytes around the trophoblasts, which clearly has a specific clonal pattern. Feto-maternal microchimerism with longstanding implanting of clonal maternal stem cells or lymphocytes in the offspring is yet another example giving rise to later autoimmune reactions both in the mother and in the adult life of the offspring. Based on the clinical association between CLL and the other malignant hematological disorders, seen as an increased frequency of the diagnoses in affected families, a genetic linking of their susceptibility seems likely. This entity of clonal disorders may then perhaps be seen as a previous feto-maternal genetic repertoire.

Keywords: Chronic lymphocytic leukemia; Malignant hematological disorders; Genetic susceptibility; Placenta; Feto-maternal reactions; Cancer genetics.

Introduction

It is a basic biological matter of fact that organ structures and organ functions, "form and function", are subjects to a constant evolutionary selection. In this process, traits of importance for the fitness, i.e. the ability to reproduce in the present environment, are maintained and further evolved while traits of no importance become rudimentary and deleted. Diversification and production of new species are part of this process [1,2]. Hence, an organism with a long evolution like Homo sapiens has been through a long accumulation of traits in benefit for the species under the given environmental conditions along with the deletion of traits, which have been useful at earlier stages but are no longer of importance for the fitness. From such a generalization, the question arises whether man in the modern, protected society is still influenced by evolutionary forces [3,4], and consequently whether Chronic Lymphocytic Leukemia (CLL), which is the most common type of leukemia among Caucasian and clearly a disease with congenital risk [5-8], is influenced by evolutionary forces. The point here is that the present day man certainly is a product of a long evolutionary selection and hence that the "form and function" of the modern man hardly present genetic traits without some importance, or rather: traits, that have been selected for the human genome because of an advantage [1-4].

CLL raises the question whether the genetics behind the disease, the genotypic congenital susceptibility, is the result of selection of genes which are an advantage to man? One would perhaps immediately think that CLL is the result of an error mechanism late in life caused by "age-dependent" mutations in lymphocytic progenitor cell at the differential pathway from where the CLL monoclone is generated. However, with the increasing knowledge on the genetics of CLL, and with CLL as the prototype of malignant lymphoproliferative disorders, we know today that CLL is no random-mutation disease [5-9]. A number of congenital risk alleles have been shown to represent the inborn susceptibility in the form of the genetic code necessary for the mutation [10-14]. From all what we know today the mutation behind the generation of the malignant CLL monoclone depends on the presence of this inherited genotype of susceptibility which seems to have a non-Mendelian segregation in affected families [15], a marked male predominance [16], ethnic predisposition [16], and signs of epigenetic parental imprinting [17-21]. The association between CLL and other malignant lymphoproliferative disorders [22,23], and a small, yet significant number of myeloproliferative disorders [15] indicate that most likely, a linked multi-risk gene complex is on question. This explains perhaps why no clear Mendelian pattern can be seen in the transgenerational inheritance of these disorders, because a clear Mendelian mode of segregation (dominant, recessive, X- or Y-linked etc.) was originally related to monogenes with marked penetrance.

This, indeed, is far from a random-error mutation disease, but clearly shows signs of a complex genetic master. It is nearly unthinkable that such a system in a species like man, at a top position of the natural selection, should have no beneficial effect, and no positive selective force to fitness. Therefore, it is relevant to put the question, where in life is the mobilization of a lymphoid monoclone advantageous? One obvious answer is the fetal life and the increasing focus on physiological viral affinity for placenta. One example is the physiological expression of retrovirus in fetal trophoblasts and the fascinating effect of endogenous retrovirus in the production of placenta- specific transcripts of several genes [24-26]. In this process the RNA of endogenous retrovirus undergo revers transcription into

double stranded DNA and become part of the genome of the germ lines of egg and sperm. Without further infection, endogenous retrovirus is able to transfer via gamets from parent to offspring in many generations. In contrast, exogenous retrovirus is present in the genome of somatic cells. Since the production of sperms is a longstanding process while the production of eggs is restricted to a short period of female embryonic life, males are supposed to be more exposed to the effect of endogenous retrovirus and thus more prone to provide placenta specific transcripts of genes promoted by retrovirus if no parental genomic imprinting takes place [26-28]. The presence of endogenous and exogenous retrovirus and monogenic transcripts in the placenta together with transgenerational transcripts from many generations of affected families undoubtedly represent a tolerated balance between genes from mother-fetus and fetus-mother with a pronounced risk of infection if no very sufficient immunological surveillance were present [29-31]. Innate immunological defects, e.g. lack of mannan-binding lectin prove the relationship between such immunological defects and abortions [32,33]. In this scenario, the interaction of gene specific, monoclonal lymphocytes in the form of mature maternal lymphocytes seem indispensable and lymphocytic infiltrates in the infected placenta are seen accordingly (Figure 1).

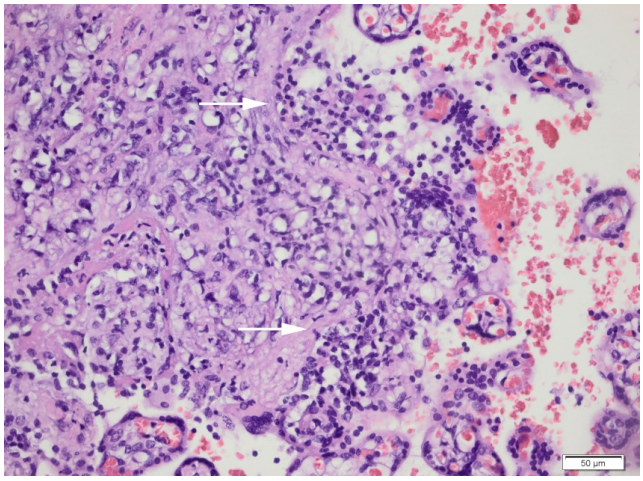

Figure 1: Severe chronic lymphocytic villitis in a third trimester placenta. Arrows show agglutinated terminal villi with necrotic trophoblast and infiltration by lymphocytes . Hematoxylin-eosin x 200

There is a striking match between the genetics of CLL [15,17,18] and the way genes can use retroviral promotors for the production of placenta specific transcripts (non-Mendelian transgenerational segregation, male predominance, and epigenetic parental imprinting). That may be interpreted as a "form and function" in common. "Bad for the postnates, good for the prenates" is the title of a textbook chapter dealing with genetic functions [34], e.g. type I diabetes mellitus, that is bad for postnates but maintained at high frequency because at some stages of the fetal life, a diabetogeneic growth pattern represent a selected advantage to the fetus [34,35].

CLL may well be seen by analogy with this mechanism: a feto-maternal need for monoclonal reaction or at least monoclonal surveillance of the physiological processing of retrovirus and their transcripts, and the risk later in life to express these genes. A need so strong that natural selection has preserved this function in spite of the risk for CLL later in life but mainly after fertile age. We are just at the beginning of this area, and many questions are awaiting an answer but both examples concern induced patterns of growth factors with a crucial fetal function.

The interaction between the potent immune system of the mother and the delicate innate system of the fetus provide defense and reactions against each other at the same time. If no tolerance were achieved, mother would destroy fetus. Tolerance denotes here regulation or silence of a great number of immune functions. Examples are the maternal production of antibodies against the paternal HLA of the fetus which are, however, not harmful. Down regulation of cytokine reactions affecting the cytotoxic T lymphocytes, killer NK lymphocytes and macrophages in the placenta, together with a number of other very specific functions, for review see [36]. In the normal polyclonal immune response of the pregnant woman, a number of humeral and cellular functions here and there at different clonal levels in the polyclonal symphony are orchestrated in such a way that mother and fetus tolerate the antigens of the feto-maternal complex, and that mother and fetus are protected from infections. The repertoire of infectious antigens is smaller in fetal life than after birth [36]. However, protection against specific and highly potent antigens such as lymphotropic herpes virus and unbalanced endogenous-exogenous retrovirus is highly needed. Instead of a general mobilization of the whole interacting immune system of the mother coordinated with the innate immune system of the fetus, a restricted purposive defense involving only those clones relevant to the specific antigen would case less systemic danger. Thus, not all, but only specific immune functions are regulated into beneficial monoclonal or oligoclonal functions during the pregnancy.

A bi-directional traffic of lymphocytes between mother and fetus is well described in the normal pregnancy [37,38]. In some cases, this traffic cause fetal engraftment with maternal stem cells and lifelong feto-maternal microchimerism [39-41]. In this way the mother can transfer specific, clonal traits from her own "self" to the offspring which later in adult life has been attributed to the pathophysiology of autoimmune, connective tissue diseases [39-41]. This could be yet another beneficial oligo- or monoclonal reminiscence from fetal life.

From knowledge available today, CLL and the other malignant lymphoproliferative disorders are linked with regard to their inherited susceptibility, seen in affected families as an increased frequency of all the diagnoses and even with a slightly increased frequency of myeloproliferative disorders. In familial CLL for instance, defined as a family with two or more cases of CLL, we also see an increased frequency of other malignant hematological disorders [15]. Familial malignant non-Hodgkin's lymphoma has a diversity of subsets of lymphomas [22], and familial Hodgkin's lymphoma is mixed with CLL and other lymphoproliferative disorders [42,43]. Multiple myeloma related to CLL has been discussed [44]. This pleiotropic co-expression may well be interpreted as a linked, congenital predisposition to monoclonal lymphocytic growth. In agreement with hereditary linked co-expression, genome-wide association studies confirm the existence of a mosaic of susceptibility loci to CLL [45], shared susceptibility to follicular lymphoma and diffuse large B-cell lymphoma [46], and specific risk loci for Hodgkin's lymphoma [47] associated with HLA [48]. Genetic anticipation [49] may be the mechanism to preserve these advantageous and selected traits down through the generations. If so, this linking between the malignant hematological disorders may then perhaps reflect a united genetic repertoire from the feto-maternal period of life.

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