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Views and Suppositions About Malarial Infections in Cancer Development and Progression

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Abstract

Burkitt lymphoma (BL) is an aggressive non-Hodgkin lymphoma. The prevalence of BL is ten-fold higher in areas with stable transmission of Plasmodium falciparum malaria, where it is the most common childhood cancer, and is referred to as endemic BL (eBL). In addition to its association with exposure to P. falciparum infection, eBL is strongly associated with Epstein-Barr virus (EBV) infection (>90%). This is in contrast to BL as it occurs outside P. falciparum-endemic areas (sporadic BL), where only a minority of the tumors are EBV-positive. Although the striking geographical overlap in the distribution of eBL and P. falciparum was noted shortly after the first detailed description of eBL in 1958, the molecular details of the interaction between malaria and eBL remain unresolved. It is furthermore unexplained why exposure to P. falciparum appears to be essentially a prerequisite to the development of eBL, whereas other types of malaria parasites that infect humans have no impact. 1 Researchers have found that the damage to DNA caused by malaria parasite in cells increases the risk of those cells turning into cancerous cells. Burkitt's lymphoma – a B cell cancer – has previously been epidemiologically linked with malaria endemic areas. Burkitt lymphoma (BL) was first described by Denis Burkitt in the 1950s. While working in Uganda, he observed numerous children with large jaw tumors (usually observed in endemic BL), subsequently noting that the geographical distribution of these tumors tended to correspond to that of malaria. BL has been associated with Epstein-Barr virus (EBV) infection; however, given that EBV is found ubiquitously, EBV infection alone does not explain the burden of BL in Africa but rather, is hypothesized to act as a co-factor for BL along with malaria infection. 2 In our article we try to find the correlation between plasmodium falciparum infection and rising rate of endemic Burkitt lymphoma in African countries from the point of view of karyogamic theory.

On the basis of experimental data and information in the literature, one possible basis for the initial tumor cell is a hybrid originated by means of the fusion of two normal somatic cells, there can be created perforations of the plasma membrane. Pores of some definite sizes can lead to the fusion of cells. In the first stage of carcinogenesis (initiation), as a result of a fusion of nuclei, a so-called precancerous sinkaryons with a tetraploid set of chromosomes may be created. Such types of cells can exist in the tissue for a long time. At the stage of promotion they can be transformed into full tumor cells under any perfect carcinogens or promoters. 3

Keywords: Fusogeny; Dikaryons; Sinkaryons; Malignization

1. Introduction

In our opinion, the mechanism of action of plasmodium falciparum on target cells is the destruction of the plasma membrane (induction of different types of perforations) and finally the fusion of somatic cells and the development of karyogamy. From the position of karyogamic theory, the action of any carcinogens is not associated directly with the

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gene apparatus of cells. Alteration of the cell's genome is induced indirectly; that is after the somatic cells' fusion and arising precancerous, tetraploid cell.

As it is known, somatic cells never interact. There is always space between them which is approximately 100-200 Å. The balance between attraction and repulsion should be maintained at this interval. If for any reason the interval becomes less than 10 Å, the formation of Ca bridges is starting leading to the long-term adhesion of the cell. Intercellular contacts are predominantly determined by two main forces; Van Der Waals positive taxis) and electrostatic (negative taxis) forces contributing to the formation of membrane electric potential. As the rigidity of leucocyte's plasma membranes is higher, it is possible that during the destruction of erythrocytes by plasmodium falciparum in leucocytes damages plasma membranes and pores of definite size, which may promote the process of fusion of somatic cells, may be formed. Larger perforations induce considerable destruction of cells' membranes and the following cytolysis together with the perishing of these cells. It seems that pores in the plasma membrane on the somatic cells formed by the action of plasmodium falciparum, substantially decrease the negative charge of the plasma membrane. Perforations lead to the weakening of the electrostatic forces and enhancement of the Van der Waals forces helping somatic cells to overcome intercellular forces and enter into contact with each other. In the case of prolonged contact adhesion process will start to develop, ⁴ which frequently especially upon the coincidence of the perforated parts, may serve as a prerequisite to fusion. At this stage, together with multinuclear cellular structures, the binuclear-hetero- or homokaryons-carriers of high carcinogenic potency are formed. As a result of karyogamy, i.e. after synchronous mitosis or simple mechanical assembly of nuclei heterokaryons (or homokaryons) mononuclear hybrid precancerous cells develop, with tetraploid (or hypo tetraploid) set of chromosomes on the initial stage of hybridization. Received as a result of somatic hybridization, the hybrid synkaryon is an initiated, immortal, precancerous cell, which exists in macro organisms indefinitely for a long time. At the initiated stage of its formation, tumor synkaryon possess a tetraploid or hyper tetraploid set of chromosomes. Fusion immediately doubles the number of chromosomes, thereby decreasing the chances that the loss of some chromosomes will kill the hybrid cell(synkaryon of stage 1) Further, in the processes of promotion and tumor progression, after the segregation of some chromosomes, there may arise tumorous cells with aneuploid or even hyperdiploid set of chromosomes. In extremely rare cases, tumorous cells possess even diploid, hypodiploid, or even hyperdiploid sets of chromosomes.

On the promotion stage, after the influence of full carcinogens or promoters on tissue (in our case P agent plasmodium falciparum), where precancerous synkaryons preexist, in these cells the chromosomal aberrations of different types and gene amplifications may arise. One of the conditions in the formation of both precancerous and tumorous cells is quantitative aberrations of chromosomes. After the invasion of Plasmodium falciparum, it seems that lymphoid cells contact with each other, following adhesion and fusion. Plasmodium falciparum has high lymphotropic abilities and is a strong fusogenic agent. In the process of tumor progression, segregation of some chromosomes in the tumorous synkarion, and also the involvement of last cells by means of fusion of a considerable amount of other tumorous cells and normal cells of different types and maturity take place. After this tumorous cells with extreme polymorphism of karyotypes and new abilities, arise. Tumor substrate originates from one synkaryon, or despite its clonal character, in most cases, the tumorous cells of highly morphologic and cytogenetic polymorphism originate.

In distinction from the generally accepted modern views in oncology, which consider that initiated agents influence the cells' genotype, by the karyogamic theory of carcinogenesis, initiated agents in the first instance interact with the cell plasma membranes, inducing their perforations, fusion process, and only then cells somatic hybridization (i.e. quantitative aberrations of chromosomes). ⁵

2. Conclusion

Here we are trying to answer one question in oncology from the view of karyogamic theory: How Plasmodium falciparum raises cancer risk? After the invasion by Plasmodium falciparum, the patient develops early morphological changes, in particular fusogenic processes in the lymphoid type of cells. It can be a prerequisite for the production of tumor cells and high incidences of Burkitt's lymphoma. Thus, it could be concluded that plasmodium falciparum can induce cells' malignization by means of somatic hybridization. Consequently, the hybridization of somatic cells represents itself as one of the possible mechanisms of malignant conversion.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that there is no conflict of interest.

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