Mechanisms of Tumour Escape from Immunological Surveillance

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The immunotherapy of cancer is attaining more and more importance throughout the world today, where the immunological responses of the patients are employed for the treatment of cancer. It is known that the immunological reactions play a significant role in the host resistance to tumours and the development of malignancy represents the failure of such host resistance. Available data indicate the existence of numerous possible effector mechanisms operating concurrently to limit the growth and dissemination of tumours. These mechanisms are responsible for the surveillance, for maintaining the integrity of structure and function in tissues and for eliminating phenotypically wayward cell clones[1].

Immunological Surveillance

After an extensive survey of known facts Burnet[2-5] put forward the immunological surveillance hypothesis, which states that "the heterogenisity of histo-compatability antigens and the associated capacity of the immunological apparatus of higher vertebrates to distinguish self from non-self is concerned with the elimination of somatic mutations." This hypothesis is further supported by the facts that (1) individuals with congenital defects in immunological responsiveness especially cell mediated immunity show a greately increased incidence of malignant tumours[6]. (2) The widespread use of immunosuppressive agents lead to malignant tumours[7] and (3) The immunological status of tumour-bearing patients is found to be low[8, 9]

The failure of immune surveillance need not necessarily lead to overt malignancy. In viral oncogenesis, immunosuppression can enhance the rate and number of tumours induced[10]. Macrophages also play a vital role in the immunological surveillance mechanism[11].

Immunological escape

Even though tumour specific immunological mechanisms are

significant factors in host resistance, the very existence of antigenic tumours implies that neoplastic cells have escaped the immunological surveillance mechanisms, or that the immune response has been ineffective. There are many theoritical possibilities by which the host reactions may be depressed and the tumour grows. Some of them are reviewed below.

1) General decline in immune capacity

Malignancy is generally associated with old age and this may be due to the decline of immune surveillance or because of the accumulation of carcinogenic impacts. It was shown that tumour isografts are better accepted in older animals[12]. Eilber and Morton [13] had shown that patients with general hyporeactivity have more rapidly growing tumours and have poorer prognosis following surgical treatment. It is well known that as age advances, the regenerative potential of lymphocytes is decreasing.

2) General immune suppression

A general depression of cell mediated immunity is noticed in lymphomas and leukemias,[14,15] and later on, in all types of advanced malignancies [13, 16]. Many chemical carcinogens have immunosuppressive action.[17, 18] Immunosuppressed patients are more prone to malignancy, as often reported in renal transplant recipients.[19] However, depression in immunity is a cause or effect of the cancer growth, is a question not yet answered.

3) Specific Immunologcal Tolerance to tumours

This may be another reason for the non-rejection of tumours. This is demonstrated by the vertical transmission of the virus through milk to the offspring rendering them tolerant to mammary carcinoma[20], Gross Leukemia[21] and Moloney Leukemia[22]. Graham and Graham[23] showed a tolerance inducing agent in human cancer tissues. Possibly the excess of antigens produced by a large tumour mass could also paralyse the host response.

4) Insufficient antigenic stimulus

Inocula of small numbers of chemically induced tumours would develop in syngenic hosts, that are capable of inhibiting the growth of medium sized, but not of a large inocula.[24] In the early stages of tumour growth, a few isolated tumour cells may present too little antigen to sensitise the host. By the time any response has become established, the tumour cells may well have replicated several times, and now the cell mass is beyond the capabilities of immune rejection.[25]

5) High growth potential of tumour cells

Tumours may replicate very rapidly to outstrip the proliferative

potential of the lymphoid apparatus. Ultimately, the dynamic nature of the growth potential of the tumours versus the immunological resistance determine the fate of tumours.[26]

6) Development of Immunoresistance

Continued use of antibiotics will lead to the selection of resistant micro-organisms. Similarly, presence of anti tumour antibodies will lead to destruction of sensitive tumour cells; but at the same time causes selection and consequent emergence of resistant tumour cell colonies. Progressive accumulation of Ig G on the tumour cell surface in a recurrent Burkitts lymphoma has been observed.[26] Globulin coating in vivo of Ehrlich's ascitis carcinoma cells has been noticed by Thunold.[27] Antibody induced suppression of the synthesis of membrane linked antigen has been demonstrated in tissue culture.[28]

7. Antigenic loss

Closely related to the above mechanisms, is the loss of antigens from the cell surfaces of malignant cells. Green[29] proposed that cancer cells were malignant because they lost tissue specific antigens and thus were no longer subject to tissue homeostatic control mechanisms. Antigenic deletion has also been shown in hamster renal carcinoma, rat muscle tumour[30] and also in human malignancies such as squamous cells carcinoma[31] gastric carcinoma[32] and kidney carcinoma[33]. Those cells which have lost their antigenicity will naturally escape from the immune attack.

8. Escape from allogenic inhibition:

Allogenic inhibition is seen to be operative only when the number of tumour inoculum is very small at the order of 10^3 to 10^5 cells[34, 35] Mammary carcinoma was rejected when inoculated in a small dose but escaped rejection when large inocula were tested[36]. Herberman et al[37] showed that the amount of antigen presented, the method and route of antigen administration, and the persistence of the antigen, all appear to be important factors in immunogenecity.

9. Immunological sanctuaries:

Tumours may arise in regions of the body hidden from the surveillance of hosts immune system. Such a mechanism has however been able to explain carcinogenesis caused by plastic films in animals[38] or asbestose in humans.

10. Antigenic concealment by carbohydrate moieties:

Carbohydrate rich proteins containing sialic acid moieties conceal the cell surface antigens and prevent detection of tumour cells by the host immune system[39, 40]. In favour of this hypothesis, it was

shown that treatment of malignant cells with neuraminidase (which will release the sialic acid from cell surface) increased their immunogenesity in experimental models [41, 42], as well as in human uterine cervical carcinoma[43]. Ascites tumour cells have been found to be protected from immune attack by a coating of sialomucine[39]. Antigenic determinants can be masked by the glucoprotein coating by mechanisms involving electrostatic repulsion, competitive hydrogen bonding or by colloid protection[39]. In a rat mammary carcinoma model, all the metastasizing tumours have little or no demonstratable glycocalyx, while all nonmetastasizing tumours have a thick glycocalyx[44]. Unmasking of tumor specific antigens by neuraminidase treatment and consequent increase in their immunogenicity has been utilized for successful immunotherapy against cancer in both animals and human beings[41, 45, 46].

11 Tumour enhancement by antibodies (Blocking factors)

Circulating antibodies may coat the malignant cells which prevent them from being destroyed by cytotoxic lymphocytes. Immunological enhancement was detected by the growth of tumours in foreign recipients by the passive administration of pre-formed specific antigens[47, 48]. Pretreatment of tumour cells with antiserum could protect the tumour cells from immune lymphoid cells when both are inoculated into hosts simultaneously[49]. Moreover, serum from immunized donors containing specific antibodies against tumour, and capable of excerting complement - dependent and cell dependent cytotoxicity against tumour cells in vitro is ineffective in controlling the growth of transplanted rat hepatomas and sarcomas[50]. As the tumour mass increases in size, the cell mediated immunity is seen to be suppressed[51], but the titre of specific humoral antibodies are seen to be increasing till the end[52, 53]. This implies that antibodies can enhance the tumour growth.

12 Inhibition of lymphocyte receptors (Inhibitory factors)

It was shown by Currie and Basham[54] that lymphocytes from patients with advanced cancer need to be extensively washed before their cytolytic properties are detectable. When this inhibitory material is assayed, patients with small tumors have Minimal inhibitory activity but in those with more advanced disease it is readily detectable. It was suggested that the inhibitory factor is circulating soluble tumour-antigens. Recently, it is shown that spleen cells taken

from immunized animals are sluggish to attack the cancer cells; but when the same spleen cells were cultured for 24 hours, they become highly cytotoxic to tumour cells[55]. Similar findings were noted in the case of lymphocytes taken from tumeur bearing animals also[56]. Moreover, when the supernatant from the culture was found to contain a factor which inhibits lymphocytes in their carcinolytic action[56]. The antigens released from tumour cells can effectively combine with the receptors on the effector lymphocytes, thereby inhibiting their action. Inhibition of lymphocyte activity by circulating tumour antigenes or by antigen-anibody complexes is demonstrated in many animal models[57-60].

These are the potential escape routes for tumours; but at present we are not able to find out which of these are important in the tumour bearing patients. We should always bear in mind that there may be alternative pathways for tumour escape such as presence of inhibitory lymphocytes, feed back inhibition by antibodies etc. Once we are able to find out the escape route, the early detection and treatment of cancer will be easier.

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