

Overcoming the problem of the lack of an immune response to cancer: A possible haptogenic approach to cancer immunotherapy

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Abstract:

Cancer cells possess a number of unusual features, most of which are explicable in the light of the theory of epigenetic carcinogenesis. This includes the remarkable failure of malignant cells to evoke an immunological response from the host which is ascribed to their deviant behaviour resulting from anomalous expression of normal gene products. Given this background a possible approach to eliciting a specific anti-cancer immune response is proposed which involves selective haptention of an identifiable target protein.

Key words: epigenetics, malignancy, melanoma, haptogenesis, immunology

Introduction:

The theory that the fundamental pathogenesis of cancer involves initiation by somatic mutation of genes that are responsible for the copying of the epigenetic pattern of differentiated cells during mitosis [1-3] is consistent with the evidence of major epigenetic abnormalities associated with cancer [4-6] and is remarkably powerful in enabling several unique and puzzling features of malignancy to be explained.

Cancer incidence reflects size and proliferation rate of tissue stem cells

Because the proposed defect is envisaged as resulting in inaccurate copying of the epigenetic pattern during mitosis the association with the proliferation rate of stem cells is explained. Malignancy is rare in slowly proliferating tissues but relatively common in rapidly renewing tissues such as epithelia and the cancer incidence in proliferating tissue is related to factors that control the rate of turnover, such as the effect of hormones on tissues like the breast [7]. Furthermore, there is evidence to show that the cancer incidence is a function of the turn over and number of stem cells that comprise a tissue [8]. All these observations are consistent with the existence of an abnormality of the type described by the theory of epigenetic carcinogenesis.

Initiation is consistent with the involvement of a limited number of somatic mutations

The epigenetic carcinogenesis mechanism is consistent with a limited number of initiating somatic mutations as embodied by the model of cancer incidence of Armitage and Doll [9]. It seems likely that the initiating defect arises in some essential epigenetic replication mechanism such as the copying of the DNA methylation pattern [10-13] and may possibly also involve failure of some quality control process such as the p53 mechanism [14-17]. Thus, assuming homozygosity, as little as 4

mutations could suffice to generate an initiated cell as suggested by mathematical modelling [18, 19].

The progressive nature of the basic error permits the explanation of multiple anomalies

Epigenetic carcinogenesis explains the observation of the multitude of genes that have been shown to be expressed in cancer cells. Malignancy is associated with a remarkably wide range of alterations in genetic expression including over- and under-expression of products that are normally associated with the tissue of origin such as the many oncogenes and tumour-suppressor genes that have been observed in various cancers [20], but also the production of proteins that are normally silenced. These observations are consistent with the proposed defective epigenetic control of gene activation, including the loss of the specific gene silencing pattern found in differentiated cells.

Epigenetic carcinogenesis accounts for the genomic instability which is a fundamental feature of cancer cells

The cytological diagnosis of cancer rests on a number of unusual criteria. The features of malignancy include cellular enlargement, increased nuclear/cytoplasmic ratio, nuclear hyperchromasia, prominent and large nucleoli, abnormal distribution of nuclear chromatin, the presence of abnormal mitoses, as well as nuclear membrane abnormalities and cellular and nuclear pleomorphism. These criteria essentially reflect various aspects of chromosomal instability (CIN) which include chromosome doublings, chromosomal fragmentation and other abnormalities occurring during mitosis which result in large-scale chaotic changes to the genome of cancer cells [21]. All these characteristics derive from abnormalities in the structure of the chromatin. Chromatin is the ultimate carrier of heritable epigenetic information. The packaging of chromatin is dependent on the structure of nucleosomes mediated through modification of histones. This in turn is directed by the local pattern of

DNA methylation, which is thus the primary determinant of chromatin architecture [22, 23]. Therefore, the proposed defect in epigenetic copying postulated by the theory of epigenetic carcinogenesis provides a mechanism to account for this feature.

The theory explains the apparent hypermutability of malignant cells

Given that the primary defect envisaged is one that results in error-prone epigenetic copying it would be anticipated that new faults can arise at each mitosis. Such a process inevitably generates an expanding spectrum of abnormalities as the affected clone proliferates and simulates the behaviour characterised as hypermutation [24,25] and suggests an evolutionary progression in which the most successful variants, such as those cells with more rapid growth or exhibiting invasive and metastatic properties, are selected which is consistent with the observed pattern of malignancy.

The notable absence of an immunological response to cancer

As noted by Burnet [26], given the extensive range of abnormalities associated with cancer cells, it is remarkable that there seems to be no general immunological response by the host to their presence and this is a matter that has provoked a great deal of comment. A great deal has been written about the possibility that part of the malignant syndrome includes the ability to interfere with the immune response and much effort has gone into investigating the various immune 'checkpoints' that enable malignant cells to escape detection by antibodies or cytotoxic T-cells [27]. But it follows logically from the epigenetic carcinogenesis theory which proposes that the emergence of abnormal properties is due to the anomalous pattern of expression of normal genes, a phenomenon which would not be expected to elicit an immune response. Some success has been demonstrated by the action of synthetic antibodies against a mutant form of the Braf oncogene [28], but this does not address the fundamental problem.

From an immunological point of view, the difficulty posed by the notion that the abnormalities exhibited by cancer cells derive from the anomalous pattern of expression of genes and not due to the abnormality of the genes themselves, is that it lacks a process that renders the products of the abnormally expressed genes immunologically recognizable. To bring this about requires a means of generating neo-antigens that will render the malignant cells 'visible' to the immune system.

Selective Haptenation as a general approach to cancer immunotherapy

One possible solution to this quandary is to selectively haptenize one or more gene products that are constitutively expressed in malignant cells. Targets could be products implicated in the faulty epigenetic processes involved in rendering the cells abnormal, or one of the re-expressed gene products that endow the cells with their malignant potential. At present these targets remain obscure but the possibility of engaging the attention of the immune system by selective haptenation has been demonstrated in melanocytes as detailed below.

The initial studies emerged from work in identifying the mode of action of externally applied agents that resulted in skin depigmentation. It had been shown by Oliver et al. [29] that contact with the monobenzenyl ether of hydroquinone resulted in marked local depigmentation. A subsequent series of studies demonstrated that a series of phenols possessed a similar action, that the effect was dependent of their oxidation by the melanocytic enzyme tyrosinase, and that the depigmentation was the result of the elimination of melanocytes from the affected skin [30-35]. Initially it was considered that this was due to a direct melanocytotoxic action of the quinone oxidation product of the active agents.

The tyrosinase-specificity suggested a possible therapeutic strategy for the treatment of melanoma and a preliminary clinical trial was instigated in which 4-hydroxyanisole (4HA) was infused intra-arterially. Morgan et al. [36] reported a clinical pilot study in which 4HA was administered to a group of melanoma patients with widespread disease unresponsive to other therapies. Despite the high doses administered, the acute responses were disappointing, suggesting that there was negligible direct cytotoxic action [35]. However, longer term follow-up showed that 45% of cases showed some degree of regression of tumours in the infused zone. There was no evidence of a generalised tumour response or of any distant cutaneous or ocular depigmentation. In one case there was complete regression of secondary tumours in the infused limb. This patient, with multiple recurrences at the site of a skin graft on the left leg, received two courses of 4HA (100 and 84 G by intra-femoral infusion) with a 4-week interval and, when seen 4 weeks after the second infusion, was tumour-free [37]. This delayed reaction would be explained by the initiation of an immune response specific to tyrosinase-expressing cells exposed to 4HA.

It had been observed that the loss of epidermal melanocytes resulting from the local application of depigmenting phenols that the absence of melanocytes was associated with an increase in epidermal Langerhans cells [38] and it was proposed that this indicated the involvement of an immune response. Further investigations led to the proposal of an immune mechanism to account for the loss of melanocytes based on the haptenation of melanogenic proteins.

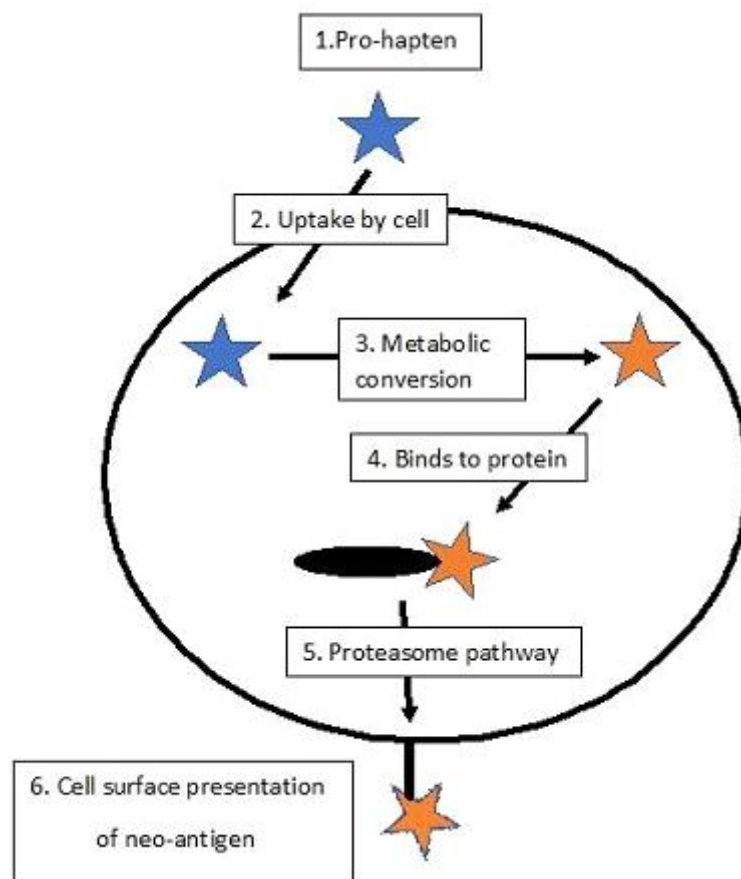


Figure 1: Schematic outline of the six stages of the selective haptention process.

In brief, the proposed mechanism involves the oxidation by tyrosinase of the depigmenting phenol forming the ortho-quinone derivative. These compounds are known to be highly reactive and undergo facile nucleophilic addition reactions [39] binding to adjacent proteins including the enzyme itself. It has been demonstrated, using tritiated 4HA, that the product is covalently bound to tyrosinase [40]. It is proposed that the haptentized proteins are processed by the proteosomal degradation pathway and the neoantigenic products exposed at the cell surface [41]. Here they are recognised by local antigen-presenting cells such as Langerhans cells and this initiates an immune response that includes cytotoxic T-cells which eliminate the melanocytes bearing the haptentic antigen. It has been argued that this is the pathological process underlying vitiligo [42] which is regarded as a manifestation of an autoimmune disease initiated by the haptention of melanosomal proteins. Since the majority of melanomas express tyrosinase activity, such a targeted haptention mechanism would account for the results obtained in the preliminary clinical trial of the anti-melanoma treatment and constitutes the mechanistic basis of the melanocyte-directed enzyme prodrug therapy (MDEPT) [43, 44]. The general process is outlined in Figure 1.

Conclusion.

This approach suggests that a similar haptention process could be employed as a therapeutic modality where a suitable expressed enzyme or specific protein target can be identified in the malignant cell population. Spontaneous regression of widespread malignancies, although a comparatively rare occurrence, might suggest that such specific haptention does take place, since a generalised immune response cannot be explained by a mutation that would affect all the

clonal variants present in metastatic cancer. Thus, it is suggested that targeted haptention could furnish a general means of eliciting anti-cancer immunity and might prove practical as a possible therapeutic strategy.

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