

# Biological Considerations of Tumor-specific and Virus-associated Antigens of Human Breast Cancers<sup>1</sup>

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## Summary

*In vivo* and *in vitro* studies bearing on tumor-specific and viral-associated antigenicity of human breast carcinomas were reviewed with particular attention to the following clinical considerations: (a) breast carcinomas arise in a nonrandom fashion; (b) *in situ* carcinomas precede invasive breast carcinomas; (c) invasive breast carcinomas behave in a heterogeneous fashion. Microscopically demonstrable lymphoreticuloendothelial responses, skin window tests, and leukocyte migration tests all indicate that tumor-specific antigenicity develops in association with the early phases of mammary carcinogenesis. Such antigenicity is maximally expressed in *in situ* carcinomas without associated invasive breast cancer and minimally in invasive breast cancers with metastases. Immunogenic breast cancer tissues commonly contain a protein component the antigenic and physicochemical properties of which are similar to those of a protein component of murine mammary tumor virus.

Advances in our understanding and control of human mammary carcinogenesis and biological behavior are dependent on the clinicopathological characterization of individual patients and their breast tissues as well as on the analytical procedures used.

## Introduction

The use of the singular designation, breast cancer, in contrast to the plural form, breast cancers, is so universal that nonclinical investigators, epidemiologists, biochemists, immunologists, virologists, etc., often come to believe that their precise techniques are being applied to precisely defined homogeneous test materials. Even clinical investigators commonly conduct their studies or apply therapy as if they were dealing with homogeneous populations. In this presentation we shall call attention to: (a) the nonrandom development of human breast carcinomas (19, 23), (b) the characteristics and biological significance of preinvasive breast carcinomas; and (c) the heterogeneous behavior of invasive breast carcinomas with particular relation to tumor-host interactions. It will be shown that clinicopatho-

logical individualization of patients and their lesions are of critical importance in investigations of mammary carcinogenesis and behavior (2). Such individualization is particularly pertinent to studies of tumor-specific and viral-associated antigens.

## Immunogenicity

PCM<sup>3</sup> and ISC occur both independently and in association with invasive breast cancer. Details regarding the diagnostic characteristics of PCM and ISC may be found in the reports of Black *et al.* (6) and Black and Chabon (8). These authors also called attention to the frequent occurrence of L-RE responses to such lesions (3, 7-9). The L-RE responses may take the form of diffuse LI and/or PVI in the region of the involved portion of the duct system. LI responses commonly include plasma cells locally and are usually associated with follicular hyperplasia in the draining lymph nodes, while PVI responses are commonly associated with SH in the regional lymph nodes.

L-RE responses appear to be structural representations of hypersensitivity (1, 2, 4, 16, 21). This conclusion is further documented by means of skin window tests using autologous *in situ* breast cancer tissues as targets (11, 12). While the foregoing observations strongly suggest that mammary carcinogenesis is associated with distinctive antigenic characteristics, they do not *per se* prove that such changes are biologically significant. It is, therefore, of great conceptual and practical importance that numerous studies have demonstrated the prognostically favorable significance of LI, PVI, and SH (1, 2, 15, 18, 21). Also, LI and SH responses are more regularly associated with breast cancers in Japanese women as compared with breast cancers in Western women (20, 24). Not only is breast cancer infrequent among Japanese women, but Japanese breast cancer patients have superior stage and survival characteristics. Thus, the structural and biological observations suggest that tumor-specific immunogenic changes influence the course and possibly the development of mammary carcinoma.

As shown in Table 1, L-RE responses to ISC are most regularly found when such lesions occur independently of invasive breast cancer, and they may be lacking in an appreciable proportion of those ISC associated with invasive breast cancer. It is also evident from Table 1 that the type

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<sup>3</sup> The abbreviations used are: PCM, precancerous mastopathy; ISC, *in situ* carcinoma(s); L-RE, lymphoreticuloendothelial; LI, lymphoid cellular infiltration; PVI, perivenous infiltration; SH, sinus histiocytosis; MI, migration indices; MuMTV, murine mammary tumor virus.

Table 1

*L-RE responses to in situ carcinoma without associated invasive breast carcinoma, and L-RE responses to in situ carcinoma associated with invasive breast cancer: relationship between L-RE responses to foci of in situ and invasive breast cancer in the same breast*

The maximal response level is to *in situ* carcinomas in Stage 0 patients > *in situ* carcinoma with associated invasive cancer > invasive cancer. Response to the latter is correlated with responsiveness to the associated *in situ* cancers.

Invasive	<i>In situ</i>			Total
	LI	PVI	Negative	
No	8 (22) <sup>a</sup>	26 (72)	2 (6)	36 (100)
Yes	31 (24)	41 (32)	56 (44)	128 (100)
	↓	↓	↓	↓
LI	17 (55)	2	1	20 (16)
PVI	7	29 (71)	2	38 (30)
Negative	7	10	53 (95)	70 (55)
Total	31 (100)	41 (100)	56 (100)	128 (100)

<sup>a</sup> Numbers in parentheses, percentages.

and frequency of L-RE responses to invasive breast cancer tissues are functions of such responses against associated ISC. It appears that immunogenicity is an early accompaniment of mammary carcinogenesis and is more regularly retained by *in situ* as compared with associated invasive breast cancers. In short, ISC and, to a lesser extent, PCM appear to possess antigenic properties that provoke prognostically favorable hypersensitivity in the host of origin. Such hypersensitivity commonly, but not universally, reacts with simultaneously associated invasive breast cancer tissues.

While tumor-specific antigenic changes seem to be regular, if not universal, accompaniments of the developmental stages of breast cancer, such antigenicity is seen less regularly among invasive breast cancer tissues. Also, the types of L-RE responses are correlated with the degree of nuclear differentiation of the cancer cells. LI responses are found almost exclusively in association with breast cancers (*in situ* and invasive) that have a low (anaplastic) nuclear grade. On the other hand, PVI responses are not preferentially associated with the nuclear grade (7). It follows that analytical studies of tumor immunogenicity should take cognizance of the structural characteristics of the tissues to be analyzed. The same caveat seems applicable to attempts to demonstrate virions or their genomic products (see below).

### Antigenic Properties of Breast Cancer Tissues

As mentioned above, skin window testing demonstrated that the vast majority of patients with Stage 0 breast cancer were responsive to autologous *in situ* breast cancer tissue (3, 11, 12). The targets in such tests were cryostat sections of the autologous tissue. This technique makes it possible to define precisely the cellular composition of the target. Cryostat sections have also been used as targets in a leukocyte migration procedure (13, 14). In such studies the cryostat sections are mounted on circular coverslips that become the roof of a Sykes-Moore chamber. The use of cryostat sections makes it possible to choose several microscopically defined samples of tissue from the same breast;

Table 2

*Response of breast cancer patients' leukocytes to autologous breast cancer tissues*

Responsiveness to the different autologous targets varies with characteristics of the target and the stage of the disease.

Target	Stage of disease	No.	MI < 0.75	MI < 0.80
<i>In situ</i> cancer	0	16	7 (44) <sup>a</sup>	11 (70)
<i>In situ</i> cancer	I	9	5 (55)	6 (67)
<i>In situ</i> cancer	II	6	2 (33)	2 (33)
Invasive cancer	I	89	26 (29)	32 (36)
Invasive cancer	II	69	15 (22)	19 (28)

<sup>a</sup> Numbers in parentheses, percentages.

namely, areas of ISC, invasive cancer, and normotypic benign areas. MI are determined by comparing the migration of the presence of the antigen with that obtained in the absence of the antigen. In our studies, detailed clinical and pathological information were correlated with *in vitro* measurements.

Table 2 presents the MI distribution according to the nature of the target and the clinical stage of the disease. It is evident that MI < 0.75 and MI < 0.80 were obtained most regularly when the target was autologous *in situ* cancer tissue from Stage 0 and Stage I cases. In contrast, such responses were least common when the target was invasive breast cancer tissue from Stage II breast cancer patients. When the target was invasive breast cancer from patients having metastases to 6+ lymph nodes, only 9 (20%) of 45 patients had MI < 0.80. Thus, leukocyte responses to autologous breast cancer tissues vary with specific characteristics of the target and with the stage of the disease.

Further evidence of the influence of target and host characteristics on responses to autologous breast cancer tissues is presented in Table 3. It will be seen that the response of leukocytes to autologous invasive breast cancer tissues, having similar nuclear grades, is correlated with the L-RE responses. Indices <0.75 and <0.80 were significantly more frequent against L-RE-positive autologous invasive breast cancer tissues than against L-RE-negative tar-

Table 3

Response of breast cancer patients' leukocytes to autologous invasive breast cancer tissue having similar nuclear grades

The *in vitro* leukocyte responsiveness is correlated with the *in vivo* L-RE responses.

	No.	MI	
		< 0.75	< 0.80
L-RE positive	62	23 (37) <sup>a,b</sup>	28 (45) <sup>c</sup>
LI positive	28	11 (39)	12 (43)
PVI positive	34	12 (35)	16 (47)
L-RE negative	74	13 (17) <sup>b</sup>	15 (20) <sup>c</sup>

<sup>a</sup> Numbers in parentheses, percentages.

<sup>b</sup> MI < 0.75,  $\chi^2$  (with Yates correction) = 5.65;  $p < 0.02$ .

<sup>c</sup> MI < 0.80,  $\chi^2$  (with Yates correction) = 8.55;  $p < 0.01$ .

gets. As shown in Table 4, leukocyte preparations that were responsive (MI < 0.80) to autologous L-RE-positive breast cancer tissue were commonly cross-reactive with L-RE-positive homologous breast cancer tissues. In contrast, leukocytes that were nonreactive to L-RE-positive autologous breast cancer tissues were uncommonly responsive to L-RE-positive homologous breast cancer tissues.

It appears from the above *in vitro* measurements that immunogenic breast cancers from different patients may share antigenic characteristics. Such antigenic similarity is a minimal requisite for the development of immunoprophylaxis. The potential for immunoprophylaxis had also been suggested by a previous study of the characteristics of breast cancers arising after prior breast lesions. If ISC and PCM are commonly immunogenic they should provoke prognostically favorable hypersensitivity in the host. Surgical resection of the local lesion would prevent the progression of the disease yet leave the hypersensitivity intact. Since subsequent breast cancers would arise in an already sensitized host, their development should be impeded if the 2nd lesions were antigenically similar to the 1st lesion. The validity of this expectation is suggested by the finding that breast cancers arising after prior removal of ISC and PCM have unusually favorable stage and survival characteristics as compared with breast cancers arising after nonimmunogenic normotypic lesions, invasive breast cancer, or no prior breast lesion (10).

Both the clinical observations and *in vitro* measurements suggest that mammary carcinogenesis is associated with immunogenic changes that are most regularly present and antigenically similar during the preinvasive phases. It would be expected that immunogenic breast cancer tissues should contain a component(s) that is lacking in control breast tissues and less regularly present in nonimmunogenic breast cancer tissues.

### Protein Components of Breast Cancer Tissue Eluates

Protein components were eluted from cancerous and non-cancerous breast tissues by incubation of cryostat sections with phosphate-buffered saline. The eluates were cleared by centrifugation and millipore filtration and then subjected to gradient polyacrylamide gel electrophoresis according to

the method of Wright *et al.* (30). A distinctive protein band was observed in 8 out of 18 breast cancer tissue eluates. This band was not observed in any of 4 samples derived from noncancerous breasts or in any of 6 samples derived from control areas of 6 cancerous breasts. Of the 8 cases in which the distinctive component was identified, 4 had the microscopically demonstrable L-RE responses. Of the 10 cases lacking this band only 4 had these characteristics.

Hollinshead *et al.* (22) used gradient polyacrylamide gel electrophoresis to separate soluble components of breast cancers, control breast tissues, and benign breast tumors. Their cancer extracts contained a prominent protein component that was lacking in the control extracts. Its migration in the gradient gel corresponds to the distinctive component that was present in our eluates of breast cancer tissues. Hollinshead *et al.* performed skin tests with proteins eluted from various segments of their gels. They found that Region 2b of their cancer extracts (containing the distinctive component) elicited positive responses in breast cancer patients but not in patients with other types of cancer. Region 2b of control tissue extracts, lacking the distinctive component, produced no response in patients with breast cancer or other types of cancer. These data, as well as our own, indicate that some breast cancer tissues contain identifiable proteins with biologically significant antigenicity.

### Response to MuMTV

The high level of antigenic similarity among ISC from different patients is suggestive of viral participation in the development of such lesions (13). In a previous report we indicated that the leukocytes of an appreciable minority of breast cancer patients responded to MuMTV-containing RIII milk but not to MuMTV-free milk from RIII and C57BL mice. We also found that preparations of isolated MuMTV were capable of inhibiting the migration of leukocytes from some breast cancer patients. Table 5 demonstrates that breast cancer patients' leukocytes that were responsive to RIII milk (MI < 0.80) were commonly responsive, on simultaneous testing, to MuMTV but not to MuMTV-free milk. Leukocyte preparations that are nonresponsive to RIII milk are uni-

Table 4

Leukocytes from L-RE-positive breast cancer patients; MI response to homologous L-RE-positive breast cancer tissues by response to L-RE-positive autologous breast cancer tissue

The responsiveness of breast cancer patients' leukocytes to immunogenic homologous breast cancer tissues is correlated with responsiveness to autologous immunogenic breast cancer tissue.

Response to autologous	Response to homologous		
	No. of tests	MI < 0.75	MI < 0.80 <sup>a</sup>
MI < 0.80			
No. of patients, 10	21	10 (48) <sup>b</sup>	15 (72)
MI 0.80+			
No. of patients, 21	43	5 (12)	10 (23)

<sup>a</sup> MI < 0.80 were uncommon when leukocytes from control women were tested against L-RE-positive breast cancer tissues, namely, 5 of 122 (4%).

<sup>b</sup> Numbers in parentheses, percentages.

formly nonresponsive to MuMTV (0 of 21), RIII milk (0 of 43), and C57BL milk (0 of 16). It appears that the distinctive responses of some breast cancer patients' leukocytes to RIII milk are related to the MuMTV content. This presumption is also supported by studies with rabbit anti-MuMTV antiserum, prepared by J. Charney of the Institute for Medical Research, Camden, N. J., against isolated MuMTV.

Of 10 leukocyte preparations from breast cancer patients that were responsive to RIII milk (MI < 0.80) 5 did not, in simultaneous tests, respond to the RIII milk in the presence of the antiserum. When isolated MuMTV was used as target, 5 of 7 leukocyte preparations responding to MuMTV alone with MI < 0.80 did not show significant migration inhibition by MuMTV in the presence of the antiserum.

### Cross-reactivity against MuMTV and Immunogenic Breast Cancer

The finding that breast cancer patients' leukocytes may respond to MuMTV is certainly of interest. By itself, however, its significance in regard to human mammary carcinogenesis and behavior is problematical. It is, thus, of interest that we observed a distinct correlation between leukocyte responses to RIII milk and to autologous and homologous breast cancer tissues (14). Further studies demonstrated that cross-reactivity was particularly frequent when immunogenic breast cancer tissues were used as the target (Ref. 17; Table 6). A further demonstration of cross-reactivity is provided in Table 7. Leukocytes that are poorly responsive to RIII milk are also poorly responsive to both autologous and homologous breast cancer tissues. Since the target tissues

were known to be immunogenic (positive L-RE response), lack of *in vitro* response would seem to reflect a lack of specific responsiveness by the leukocytes. In short, the inability of the leukocytes to respond to the antigens of RIII milk *in vitro* is paralleled by a decreased ability to respond to immunogenic breast cancer tissue. Conversely, leukocytes that react to RIII milk concomitantly react to the majority of L-RE-positive targets and to a lesser proportion of L-RE-negative tissues.

The response of RIII-negative leukocytes to a minority (approximately 20%) of autologous and homologous breast carcinoma tissues as reported previously (17) suggests that some breast cancer tissues possess tumor-associated antigens that are unrelated to MuMTV. It would be of interest to compare the biological significance of such antigens to MuMTV-cross-reactive antigenicity.

Breast cancer patients' leukocytes that were responsive to RIII milk and autologous cancer tissues, as assessed by leukocyte migration inhibition tests, cross-reacted in 10 out of 16 tests with homologous breast cancer tissue containing the distinctive protein component as identified by polyacrylamide gel electrophoresis. Table 7 demonstrates that these leukocytes responded in only 1 of 4 tests to homologous breast cancer tissue lacking this component; none of the leukocyte preparations showed reactivity to RIII milk or benign tissue from cancerous or noncancerous breasts.

Antigenic similarity between some components of human breast cancer cells and MuMTV is also suggested by the observations of Muller *et al.* (25, 26). They reported that the serum of some breast cancers contains an antibody that reacts with sections of virus-containing mouse mammary tumor tissue. Later studies showed that the antibody combined selectively with A-particles and intracytoplasmic membranes but not with mature B-particles.

The apparent antigenic similarity between MuMTV and some breast cancer tissues is paralleled by physicochemical similarities between the GP-52 fraction of RIII virus and the distinctive protein identified by polyacrylamide gel electrophoresis in eluates from such tissues (unpublished data). Both the GP-52 and the distinctive breast carcinoma-associated protein show identical electrophoretic mobility in polyacrylamide gels. Moreover, the molecular weight of this carcinoma-associated protein is similar to that of GP-52, namely, 51,500 as determined by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (A. Dion, Institute for Medical Research, Camden, N. J.).

Table 5

Cross-reactivity of RIII milk-responsive leukocytes from breast cancer patients against MuMTV, and MuMTV-free mouse milk

Breast cancer patients' leukocytes having indices < 0.80 against RIII milk commonly cross-react with MuMTV but rarely with MuMTV-free milk.

Target	No.	MI < 0.80
MuMTV	14	6 (43) <sup>a</sup>
RIII milk	14	1 (7)
C57BL milk	9	0
Swiss milk	2	0

<sup>a</sup> Numbers in parentheses, percentages.

Table 6

Response of leukocytes from L-RE-positive breast cancer patients tested simultaneously against RIII milk, and L-RE-positive autologous and homologous breast cancer tissues

No.	MI vs. RIII milk		Autologous		Homologous <sup>a</sup>	
	Range	Mean ± S.E.	< 0.80	Mean ± S.E.	< 0.80	Mean ± S.E.
11	0.34-0.79	0.64 ± 0.04	7/11 (63)	0.74 ± 0.04	18/26 (70)	0.75 ± 0.04
8	0.80-0.89	0.83 ± 0.01	1/8 (12)	0.90 ± 0.04	5/18 (28)	0.89 ± 0.04
12	0.90-1.35	1.05 ± 0.03	2/12 (17)	0.99 ± 0.04	2/20 (10)	0.94 ± 0.04

<sup>a</sup> The homologous targets were samples from 9 different L-RE-positive breast cancers. All leukocyte preparations were tested simultaneously against RIII milk, autologous breast cancer tissue and at least 1 (commonly 2 to 3) homologous cancer tissues.

Table 7

Breast cancer patients' leukocyte preparations responsive ( $MI < 0.80$ ) to autologous breast cancer tissue and RIII milk: *in vitro* testing for cross-reactivity to RIII milk, benign breast tissues, and selected breast cancer tissues

Breast carcinoma patients' leukocytes selected for responsiveness to autologous cancer tissue and RIII milk show a high level of cross-reactivity against homologous polyacrylamide gel electrophoresis-positive<sup>a</sup> as compared to polyacrylamide gel electrophoresis-negative breast cancer tissues. No cross-reactivity is observed against RIII milk and benign breast tissues from cancerous and noncancerous breasts.

Patient	Stage	Date	Autologous breast cancer tissue	RIII milk	RIII <sup>f</sup> milk	Homologous benign tissue from		Homologous breast cancer tissue	
						Benign cases	Breast cancer cases	Polyacrylamide gel electrophoresis-positive	Polyacrylamide gel electrophoresis-negative
5175-74	I	12/16/74	0.76	0.69	0.89	0.82		0.80	0.85
6210-74	0	1/9/75	0.61	0.56	0.93			0.63, 0.81	
6654-74	I	1/30/75	0.70	0.72	0.94	1.03		0.70, 0.76, 0.77	1.04
4682-72	II	2/3/75	0.72	0.77	0.95		0.93	0.70, 0.79, 0.97	
2458-72	I	2/10/75	0.76	0.75	0.96	1.18	0.94	0.70, 0.92, 1.06	
865-74	I	2/19/75	0.78	0.55	1.11			0.81	
865-74	I	2/24/75	0.61	0.57	1.01	1.03	0.90	0.59	
1431-75	II	3/2/75	0.64	0.78	0.93			0.64	0.93
6010-73	I	4/2/75	0.52	0.64	0.95			0.56	0.73
Mean			0.68 ± 0.03	0.67 ± 0.03	0.96 ± 0.02	1.02 ± 0.08	0.92 ± 0.01	0.76 ± 0.03	0.89 ± 0.07
± S.E.									

<sup>a</sup> Polyacrylamide gel electrophoresis-positive, distinctive protein component (see text) present in phosphate-buffered saline-eluates from the tissues tested.

## Molecular Hybridization

In considering the possibility of viral participation in human mammary carcinogenesis it is pertinent to take note of data derived from molecular hybridization studies. Schlom and Spiegelman (27) have reported that RNA derived from a significant proportion of different breast cancers hybridizes with DNA generated by reverse transcriptase activity from MuMTV RNA templates. On the other hand, Vaidya *et al.* (29) found that hybridization with RNA from unselected breast cancer tissues was uncommon. In view of the nonrandom development and stepwise progression of human mammary carcinomas, it would be of interest to determine whether hybridization is correlated with distinctive clinical and/or pathological characteristics of breast cancers.

## Conclusions

If all breast cancers were similar in development and biological behavior, it would be reasonable to expect uniformly positive or negative results with diverse investigative techniques, namely, epidemiological, virological, biochemical, immunological, and therapeutic. If, on the other hand, the development and biological behavior of breast cancers were influenced by constellations of exogenous and endogenous factors, it would not be surprising if different investigators, using unselected targets, obtained different answers to the same question. The failure to take cognizance of the latter possibility is responsible for many a pointless polemic. On the other hand, an awareness of the nonrandom development of breast cancer, the distinction of the devel-

opmental from the progressive phase, and an appreciation that the biological behavior of invasive breast cancers reflects complex interactions between tumor and host may allow the investigator to give meaning to his data. Equally important, such awareness allows the investigator to be perceptive of experiments of nature that provide uniquely valuable insights into the role of particular components of cancer development and behavior. A better understanding of human mammary carcinogenesis and biological behavior is no less dependent on the clinicopathological characterization of individual patients and their breast tissues than it is on the analytical procedures used.

When the available data are viewed in the light of the above considerations, it appears that immunological phenomena do indeed play a significant role in the biological behavior of breast carcinoma in individual patients. The critical variables include tumor-associated antigenicity and specific cellular hypersensitivity responses of the host. Since both characteristics are maximally expressed during the preinvasive phase, immunoprophylaxis appears potentially attainable (3, 10). On the other hand, tumor-associated antigenicity and specific cellular hypersensitivity responses of the host are minimally expressed in patients with disseminated breast cancer. Since antigenicity and hypersensitivity may vary independently, there would appear to be specific limitations to the development of effective immunotherapy of breast cancer. The point to be emphasized is the need to relate putative immunotherapeutic procedures to the characteristics of individual breast cancer patients. The same caveat is applicable to the use of immunodepressive adjuvant chemotherapy and radiation therapy (4, 5, 28).

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