Table 1. Mean serum T3 and T4 levels and SEM (in parentheses) in six groups of patients with differentiated thyroid carcinoma after hormonal therapy recommenced. Normal values for T3 are 60–200 ng/dl and for T4 5–11.8 μg/dl

Days	0	7	14	21	30	60
T3						
Group 1	37.5	57.3	66.4	80.9	97.4	125.7
	(3.8)	(9.4)	(8.4)	(7.8)	(6.1)	(10.4)
Group 2	44.8	104.8	132.5	137.3	147.8	148.1
	(6.5)	(8.3)	(11.5)	(9.5)	(9.6)	(10.4
Group 3	45.7	150.0	173.8	177.0	214.3	145.0
	(5.3)	(14.9)	(17.8)	(13.6)	(22.3)	(10.2)
Group 4	30.6	63.1	93.9	112.0	119.1	139.7
	(38.0)	(8.4)	(11.2)	(8.2)	(6.2)	(7.1)
Group 5	38.9	137.5	172.0	190.0	186.0	169.0
	(5.0)	(20.4)	(10.7)	(18.6)	(13.0)	(8.8)
Group 6	32.1	215.0	228.7	222.5	206.5	151.0
	(2.8)	(20.3)	(20.4)	(17.2)	(7.7)	(8.8)
T4						
Group 1	0.6	3.2	5.1	6.8	8.0	10.4
	(0.1)	(0.5)	(0.5)	(0.5)	(0.5)	(0.6)
Group 2	2.0	6.1	7.0	7.1	7.8	10.5
	(0.4)	(0.4)	(0.2)	(0.3)	(0.4)	(0.3)
Group 3	2.6	5.5	7.3	7.7	9.0	10.4
	(0.5)	(0.5)	(0.7)	(0.6)	(0.5)	(0.4)
Group 4	1.1	5.5	8.3	10.2	10.7	13.9
	(0.1)	(0.7)	(0.9)	(0.9)	(0.8)	(1.0)
Group 5	3.3	8.0	11.1	11.5	11.4	12.8
	(1.2)	(1.1)	(0.8)	(0.8)	(0.5)	(0.4)
Group 6	1.8	6.6	8.8	10.1	10.5	14.1
	(0.3)	(0.5)	(0.8)	(0.9)	(0.5)	(0.8)

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Prognostic Significance of Phagocytic Functions in Breast Cancer Patients

J. Lukač, S. Lechpammer, Z. Kusić, A. Bolanča and N. Daković

THE ROLE of immunocompetence in the prognosis of breast cancer has been widely examined, but to date no series of practical immunological tests has been identified which clearly permits accurate prediction of survival [1–3]. In this study, preliminary results of evaluation of prognostic significance of phagocytosis, the most important host defence mechanism, are presented. Using an acridine orange method described previously [4] and viable yeast cells as targets, the phagocytic activity (% of phagocytic cells), in addition to ingestion and intracellular killing abilities of peripheral blood granulocytes and monocytes, were determined in 66 patients (mean age 61 years) with ductal invasive breast cancer, clinical stages I, II and III (38, 40 and 6%, respectively). Assessments were made after radical mastectomy, but before proceeding with any other therapy, and repeated for a group of 36 age- and sex-matched healthy volunteers. Results were analysed using the Mann–Whitney U test. Granulocyte ingestion ($P=0.001$), granulocyte microbicidity ($P<0.009$) and monocyte microbicidity ($P=0.039$) were decreased in the patient group compared with normal values. After a 3-year follow-up, 8 patients (group B) developed distant metastases (2 liver, 2 lung, 4 bone), while the other 58 remained free of metastases (group A). Retrospective analysis of phagocytic functions determined at the beginning of the follow-up period (i.e. at the time when all patients were free of distant metastases) showed differences between these two groups. Granulocyte phagocytic activity in group B was decreased in comparison with group A ($P=0.057$). Monocyte phagocytic activity in group B was also decreased, although the difference was less significant ($P=0.103$). Further differences appeared in the monocyte intracellular killing capacity, which

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was also decreased in group B ($P=0.015$). Results presented show that both granulocyte and monocyte phagocytic functions are altered in breast cancer patients early in the disease process, and are not caused by potentially myelosuppressive therapy [5]. Differences in these functions, which existed at the time of diagnosis, seem to be related to the progression of the disease and therefore could be of prognostic value.

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A New Model for the Interaction of EGF-like Ligands With Their Receptors: the New One-Two

W.J. Gullick

OVEREXPRESSION or mutation of the type 1 growth factor receptors and their ligands occurs frequently in human tumours, and in some cases is associated with prognosis and response to treatment. A deeper understanding of their mechanisms of activation would be useful in the design of receptor inhibitors.

For some years, the accepted model for interaction of epidermal growth factor (EGF) with its receptor has been that one ligand binds to a receptor monomer, and that this is followed by receptor dimerisation, forming a complex of two receptors and two ligands (2:2). I wish to consider a new model in which a single molecule of EGF binds to a receptor dimer (1:2).

Such a complex is necessarily asymmetric as EGF itself is asymmetric. This, therefore, requires that one face of the ligand binds to one site in the first receptor (site A) and, through another part of its surface, to a different site in the second receptor (site B). Is there any reason to believe that this could occur? Inspection of the primary sequence of the extracellular domain of the EGF receptor suggests a possible explanation in that this is composed of two related sequences, each containing a region rich in cysteine residues associated with another sequence. Experiments from Schlessinger and colleagues have demonstrated that the more C-terminal (domain III) of the non-cysteine rich regions is largely responsible for ligand binding [1], but that mutations in the second N-terminal equivalent region (domain I) also, but less fundamentally, affect binding [2]. It is possible, therefore, that ligand binding occurs first to site A (domain III) in a monomer with moderate affinity, and that this is followed by dimerisation with a second receptor, but with the EGF binding to site B (domain I), thereby forming the high affinity complex.

What is the evidence in favour of this model? Mutational analysis of EGF suggests that substitution of either residue 41 [3] or 47 [4] prevents receptor recognition. However, these side chains are on opposite faces of the ligand [5]. In the 1:2 model, this would be predicted, but it is less easy to reconcile with the 2:2 structure. Secondly, in the closely related type 1 receptors, HER2 and HER3, NDF/Heregulin can be chemically cross-linked to either receptor in a heterodimer, suggesting that the ligand is in close proximity to each receptor molecule [6]. A precedent for this 1:2 complex is provided by the asymmetric structure of one molecule of growth hormone bound to two receptor proteins [7].

The principle evidence in favour of the 2:2 model is the stoichiometry of ligand binding determined by Weber and associates [8]. These measurements, despite being carefully performed, are, however, sensitive to small variations in specific activity of the iodinated EGF, and the accuracy of measurements of protein concentration by comparative Coomassie blue staining and autoradiography. The structure suggested here leads to some predictions which can be tested by experiment, which may help to resolve the issue. Binding of one ligand to a receptor heterodimeric complex would not, for instance, allow binding of another ligand. For example, EGF binding to a heterodimer of EGFR and HER3 would prevent binding of NDF/Heregulin and *vice versa*. A speculation arising from this model is that it is possible that the five different ligands, known to bind to the EGF receptor and the alpha and beta families of NDF/Heregulin (which differ in their C-terminal parts of the EGF-like element), may be able to stabilise different combinations of type 1 receptor heterodimers. I believe therefore that, for the moment, results of experiments performed on this highly interactive system of receptors should now be considered in the light of both models.

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