Differentiation and Immunology

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Differentiation and Immunology

Edited by

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INTRODUCTION: MOLECULAR SPECIFICITY—LINK BETWEEN IMMUNOLOGY AND DIFFERENTIATION[1]

PAUL WEISS

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Like organic evolution, progress in science draws on two sources. On the one hand, there is the progressive specialization and refinement within individual disciplines, comparable to the selection of adaptive mutations within species, and, on the other hand, there is the emergent novelty resulting from the crossing of formerly isolated lines to yield fertile hybrids, often endowed with hybrid vigor. Cross fertilization has been the intent of this symposium. Studies on *differentiation* and on *immune reactions* in organisms have been running in parallel and relatively independently until rather recently when signs of confluence became apparent. Although the first hybridization attempts between the two antedated the era of modern molecular genetics and macromolecular biology in general, the upsurge of these latter branches presages a firmer union between the studies of development and of immunology into a new hyphenated scientific discipline. The symposium, the major contributions to which are presented in this volume, was organized to give expression to this fact. It had a precursor in a symposium on "Immunology and Development," held twelve years ago [1]. A comparison between these two events is quite instructive. It shows that, whereas advances in technical sophistication and understanding have been made in both lines, though perhaps more in matters of immunology than of differentiation, mutual interaction has remained on a minor scale. Hopefully, this symposium will give it impetus.

Let us look briefly at what to expect from such an interaction. In the first place, since the ability to form antibodies is confined to certain cell types only, the development of the distinctive characteristics of those cells is in itself a prototype of cell differentiation, singularly suitable for rigorous analysis. Many examples of progress in this field will be found throughout the chapters of this book. Conversely, immune sera, prepared against specific tissue types, can serve, by their localized and target-specific effects, to distinguish features of differentiated tissues not dis-

[1] Original work referred to in this introductory chapter was supported in part by Grants CA 10096 and NB 07348 from the National Institutes of Health (U.S. Public Health Service) to Dr. Paul Weiss as principal investigator and by a grant from the Faith Foundation of Houston.

tinguishable by any other criteria. Moreover, as more is becoming known about the genetic basis of antigenic differences and a correlation is beginning to be made with the data of molecular genetics in their bearing on protein synthesis, further pursuit of this relationship might also yield valid models for the molecular correlates of cell differentiation in general. The prospect of success for such an explanatory extrapolation, of course, hinges on how broadly one conceives of that particular phenomenon of "differentiation" that one undertakes to explain.

For instance, one serious difficulty, not generally taken into account in current attempts to establish a cogent link between the total genic endowment of cells, on the one hand, and the typically disparate expressions of that endowment in the diverse cell types of higher organisms on the other, stems from an unwarranted confinement of interest to the phenomenon of *cytodifferentiation.* This focuses on a given cell *individual* during its conversion from a morphologically or otherwise rather undistinguished appearance into a state in which overt structural or cytochemical characters enable an observer to identify the tissue type to which the particular cell individual belongs. Thus, primitive embryonic myoblasts, chondroblasts, and melanoblasts may be almost indistinguishable until they develop their visible signal flags of muscle fibrils, cartilage matrix, or melanin granules, respectively. Various theories have been proposed to explain this process of cytodifferential expression in terms of the masking or derepression of appropriate stretches of the gene string. Yet, however adequate such theories may turn out to be as explanations of the fate of a given cell individual, they do not seem able to account for the major problem of development in higher forms, at least of animals, which is that different somatic cell types, once they have become established in their various differential characters, will keep on breeding true to their acquired characters despite the fact that they all retain essentially the same genic endowment.

Thus, *strain differentiation* gives rise to cells the offspring of which continue to breed true for generations even if reared in a common environment different from, and unrelated to, the original sites and environments in which they attained their primary differentiation [2, 3]. For instance, when cultured *in vitro,* descendants of the various explanted cell types may change considerably in their morphological and functional expressions, but the *differentials* between the progenies of the different strains continue to remain demonstrable, perpetuated without attenuation, let alone abolition. Bacteria, the prime test objects of molecular genetics, can hardly furnish us with models for the self-perpetuation of differentiation of somatic *cell strains* since the generative cell and the somatic cell in bacteria are one and the same. The magnitude of the

problem of strain differentiation becomes staggering if one takes account of the great number of intrinsically diversified cell species in a higher animal organism, detectable by cytochemical and physiological differentials, far in excess of the gross distinctions discernible under the microscope.

The categorical distinction between cytodifferentiation and strain differentiation need not imply that some common denominator for both might not eventually be demonstrated. In fact, I have in the past favored the hypothesis that the bifurcation of a single cell line into two distinct true-breeding subspecies might be inaugurated by an erstwhile reversible step of "modulation" of the common ancestral cell from which they stem in one or the other of two alternative directions. But just how the subsequent fixation of the self-perpetuating limitation could be derived simply from an automatic extension of the current molecular vocabulary proposed for cytodifferentiation is to me still quite obscure.

It is in this direction that the lessons of immunology present us with a parallel which might turn out to hold a key to the understanding of strain differentiation in a much wider sense. It lies in the phenomenon of acquired immunity (or conversely, acquired hypersensitivities), in which a cell strain, induced to produce antibodies against a given foreign antigen, continues to yield progeny matching the alien antigen long after the latter has ceased to be physically present. If the term "alien" were to be expanded to include mutually alienated (i.e., disparately differentiated) cell strains of the same organism in contact or interaction, the linkage between theories of immunology and differentiation might become close enough to serve as a point of departure for a more general theory encompassing both. Without prognosticating the eventual outcome, the pursuit of the idea, if only by the juxtaposition of parallelisms of the indicated kind, as in this symposium, seems to be worthwhile in the almost trackless wilderness in which we still find ourselves in the problems of differentiation.

Yet, the potential benefits of close association between immunology and cell biology extend way beyond the problems of differentiation. A few examples of this projection into the future, picked at random, might serve to justify this note of optimism.

Even before the days of modern molecular biology, the crux of the immunological response as symbolized in the key-lock analogy of Paul Ehrlich has been sought in the complementarity of structural (i.e., steric) properties of matching macromolecules. The course of analytical studies since has amply justified that premise. Moreover, it is becoming ever more patent that the principle of molecular complementariness extends far beyond the range of immunological phenomena, being in fact one of

the most fundamental properties of biological mechanisms. In my own attempts at finding broad common denominators and explanations for biological phenomena in areas seemingly as disparate as development, immunology, wound-healing, endocrine regulation, growth control, and the functioning of the nervous system, I have been increasingly impressed by the likelihood of reducing many puzzling problems to a single principle of steric matching, key-lock fashion, among molecular systems of *complementary structure* [4], or more generally, *complementary dynamic specifications*. Immunological interactions would merely represent one special manifestation of the same principle, perhaps more intensively studied because of its practical significance, but otherwise a co-equal beneficiary of a universal biological principle which in another version, for instance, appears in all those cell biological and developmental interactions which I have lumped under the label of template-antitemplate processes.

The factual foundations and the rationale underlying this broad generalization have been illustrated in a recent book [5], but can, of course, not be detailed here. However, since the matter, in a way, supports the rationale of the present conference, some spot examples might be briefly cited. In speaking of structural complementarity between interacting macromolecules, for instance, in the rather static structural terms originally formulated by Linus Pauling, in which the strength of bonding among molecules along two closely fitting molecular surfaces, comparable to a mold and its cast, result in the *selective* interaction between two systems, we may for the moment ignore whether the matching configuration was imposed by one partner upon the other in the manner of a true "induction" or whether the interlocking systems had been prematched coincidentally. Even if translated into modern terms of molecular conformation, this phenomenological duality in the origin of conformity remains.

However, as I indicated previously, the static concept of selectivity based on purely configurational complementarity may have to be amended further by adding complementarity of *dynamic* specifications as a candidate for key-lock mechanisms. This addition seems called for in view of the general need for loosening up some of the rather rigid static thinking that cell biology has inherited from its microscopic past, now sometimes even reaching two orders of magnitude farther down into the realm of electron microscopy. The growing isotopic evidence of very rapid turnover of macromolecular populations in the cell, denoting limited stability and durability of any one particular molecular unit per se (other than perhaps DNA) seems to demand a major shift of attention from individual molecules to molecular collectives contributing conjointly and cooperatively to ordered group performances. In the terms of what I once

outlined as "molecular ecology," the existence, survival, and operation of any one macromolecule is a critical function of the peculiar constitution and constellation of its immediate local environment, which, in turn, includes other, equally interdependent, molecular species. Macromolecular communities, therefore, are in a sense complex symbiotic groupings of members subtly harmonized to mutual coexistence, as well as to the more general pool of their metabolic requisites. Thus, if one were to consider the surface of a given cell as a metastable mosaic of such macromolecular communities (including among their members lipoproteins, glycoproteins, mucopolysaccharides, etc.) in equilibrated proportions and activity states, perhaps even yielding a resultant periodicity of their group kinetics, one could ascribe specific interactions of that cell with another cell through surface contact to the presence of matching molecular domains of reciprocal kinetic activity patterns in mutual resonance.

As one can see, the regular coded fine structure of macromolecules would then form only part of the true "information content and transmittal" in a cell; partial in that it could become effective only in combination with, and through the agency of, the pulsating or otherwise temporally structured force fields generated by group activity. I mention this highly speculative, but by no means wholly unsubstantiated, scheme merely because in the light of growing realistic acquaintance with the properties of living cells, the empirical concept of "active sites" in the cell surface for intercellular transactions would seem to be more readily amenable to some such solution as here ventured than by sole emphasis on individual macromolecules as solitary agents. At any rate, whatever the precise mechanism of selective cell interactions may turn out to be, and it may indeed operate through a variety of mechanisms employing a common principle, the ubiquity of its use in the coordination of living processes is unmistakable. It is readily documented by the following list of typical examples.

(*a*) *Selectivity on the molecular scale.* Specificity between antigen and antibody, both in their mutual recognition and selective interaction; selective relation between enzyme and substrate.

(*b*) *Selective interactions between macromolecule and cell.* Selectivity of cells for food substances, drugs, and products of other cells, such as hormones; selectivity of chemoreceptors for gustatory and olfactory stimulants.

(*c*) *Selectivity of cells for particles.* Selective phagocytosis; ingestion of food particles by invertebrate cells; selective virus penetration into cells.

(*d*) *Selective cell-to-cell interactions.* Species-specific impregnation of eggs by sperm; selective conjugation of protozoans; selectivity in the association of cells with like and complementary cell types in tissue formation; selectivity of sensory or motor nerve fibers in either making or shunning synaptic connections with receptor or effector cells, respectively; selectivity of cells, as well as of their processes (e.g., nerve fibers), for matching types of pathways in their migrations ("selective contact guidance"); selectivity of parasites for corresponding hosts.

These examples could be vastly amplified. It will be noted that almost all those listed exemplify the wide variety of biological mechanisms that rely for their target-specificity on prearranged key-lock correspondence between missile and target. Save for the example of antigens determining the configuration of the corresponding antibodies, there is little in the list that would bear directly on one of the salient questions in the differentiation problem: whether there are cases in which there is an actual "induction" of matching specificity in a more plastic cell by a more firmly structured one, implying a veritably "instructive" process, comparable to the molding of a lock to fit a given key. In general, influences of this kind have been suspected whenever a definite criterion of differentiation in a given cell type x known to be normally associated with the presence of a cell type y, failed to develop in the absence of y, but could still be brought out by the timely restitution of y. The pertinence of this simple formulation, however, is belied by the heterogeneity of processes that fit the formula. Again, only a cursory illustration of the complexity of the problem is feasible here, as follows.

The simplest cases deal with ordinary trigger effects that merely release, or rather disinhibit, a preformed further step in an intrinsic cellular reaction sequence, the trigger bearing no specific relation to the pattern of the ensuing event; in cases of this kind, the course of differentiating steps had already been single-tracked in the particular cell strain. Then there are the more strictly differentiating actions in which the "inductive" effect may result from some graded environmental conditions "tipping the scales" in a bivalent cell that is still capable of proceeding in either of two alternative, but mutually exclusive, courses. The favored course gradually monopolizes the synthetic pattern of the cell, and thereby also sets the course of its progeny. In some cases, the decisive environmental threshold might be a simple function of the inorganic content of the medium bathing the cell surface. In other cases, the triggering key action is exerted by special types of molecules (e.g., the switching of secondary