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PERITONEAL LYMPHOID CELLS

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INTRODUCTION

The peritoneal cell population is in some respects like that of connective tissue elsewhere, allowing for differences which may arise from the fact that its cells are in a fluid matrix. The study of the peritoneal cells may therefore contribute perhaps to our understanding of some of the wider problems of the connective tissues generally.

Of the non-granular cells of the peritoneum, most attention seems to have been paid in recent years to the monocyte-macrophage group, and relatively little interest appears to have been taken in the lymphoid cells. The present communication draws attention to some of the reasons for this state of affairs, and also notes some of the gaps in our knowledge of the peritoneal lymphoid cells, which present problems *sui generis*.

CELL IDENTIFICATION AND CLASSIFICATION

One of the major difficulties is that there is no clear and generally accepted classification of the non-granular peritoneal cells, as becomes evident if one considers a few of the many available examples. Carr (1) described the non-granular peritoneal cells as consisting of lymphocytes, macrophages, and mesothelial cells, the lymphocytes being either "classical small lymphocytes," or "rather larger cells, similar to previously described immunoblasts." Argyris and Askonas (2) noted small lymphocytes, medium mononuclear cells, and macrophages — with a preponderance of the cells termed medium mononuclear. Joos et al (3) recognized small lymphocytes, large lymphoid cells, lymphomonocytoid cells, monocytoid cells with round nucleus, and monocytoid cells with kidney-shaped nucleus. Fedorko and Hirsch (4) noted only lymphocytes and macrophages, the latter possessing a horseshoe-shaped nucleus, eccentrically located. Shands et al (5) refer to macrophages and mononuclear leukocytes, noting that only non-phagocytic cells were included in the mononuclear group. The term mononuclear, used by many observers, clearly covers a wide spectrum of cells.

In a recent study (6) the non-granular cells of the peritoneal cavity were provisionally regarded as consisting of six main groups: 1) Pachychromatic small lymphocytes; 2) Larger lymphocytes of varying sizes, some of which possessed markedly basophilic cytoplasm and could be regarded as blast cells, immunoblasts or otherwise; 3) Transitional cells; 4) Monocytes-relatively few in number; 5) Macrophages; and 6) a small number of what were thought to be mesothelial cells. Groups 1, 2, and 3 are usually described together as "lymphoid". The transitional cells however are a very different population from the other lymphoid cells, and present problems *sui generis (7)*.

LYMPHOID CELLS

There are marked species differences in the peritoneal cell population. In the most

commonly used experimental animal, the mouse, lymphoid cells constitute the majority of the cell population in the peritoneal cavity. Goodman (8) recorded 75-85% of lymphocytes in murine peritoneal fluid, while Balner (9) obtained a figure of 50-65% total lymphocytes, subdivided into small and medium categories. Kornfeld and Greenman (10) found 70% small and medium lymphocytes. Argyris and Askonas (2) recorded 20% large macrophages, 13% small lymphocytes, and 65% "medium mononuclear cells." Shelton et al (11) gave figures of the same general order, but emphasized the very considerable variation associated with age and sex differences. From the point of view of function, there are a number of distinct subgroups in what is usually regarded as the lymphoid cell population. Among these subgroups one may note (1) B cells (2) T cells (3) Null cells (4) Phagocytic lymphocytes (5) NK cells (6) Transitional cells.

According to Catanzaro et al (12) about 50% of normal peritoneal lymphocytes are Ig+, raising the possibility that the remaining 50% might be Ig- null cells. After the intraperitoneal injection of mineral oil only 5% of the exudate lymphocytes were Ig+. However, care must be exercised in interpreting these data, since some of these null cells may be newly-formed Ig-B cells just discharged from the marrow (13,14). It remains therefore to be established how many of these Ig- cells are really null cells, or immature B cells which have yet to mature and develop surface immunoglobulin.

Kornfeld and Weyzen (15), after repeated I.P. immunization, made a functional distinction between "determined" lymphocytes, which were not antibody-producing when collected but could develop into antibody-forming cells after transfer without further contact with antigen, and "memory" cells relatively resistant to irradiation.

T Lymphocytes

Catanzaro, Graham and Burns (12) observed that in the normal peritoneum there was a relatively small number of lymphocytes responding to T cell stimuli such as Con A or allogeneic cells, as compared with a high percentage of T cells in the spleen (cf. Raff, 16). In peritoneal exudates (17), on the other hand, there was an increased number of uropod-bearing lymphocytes, generally thought to be T cells. Rosenstreich and Shevach (18), working with guinea-pigs, noted that the peritoneal exudate lymphocytes obtained 2-4 weeks after footpad immunization consisted of an increased number of T cells.

Null Cells

Subject to what has already been stated about Ig- B cells, it would appear that non-T cells which are Ig- may contain a variable number of null cells.

Phagocytic Lymphocytes

Phagocytic lymphocytes in the peritoneal cavity have been described by a number of workers (3,5,19-21). These lymphocytes do not appear to transform into macrophages, but persist as lymphocytes. Most of the phagocytic lymphocytes are to be found among the larger lymphoid cells, though on occasion one may note a very distinctive cell, with the appearance of a typical small lymphocyte, which ingests particulate matter very rapidly and becomes heavily loaded in an unusually short time.

Natural Killer Cells

NK cells (22) are non-adherent cells which have been described as "large granular lymphocytes". Postnatally, they are thought to be formed in the marrow (23-25), from which they appear to be continually entering the bloodstream, out of which presumably they can readily enter the peritoneal cavity as well as other tissues. There appears to be considerable cytotoxic activity even in normal peritoneal cells (26), but there is a marked increase after the intraperitoneal injection of BCG (27,28) or of Corynebacterium parvum (29). A recent study of athymic rats (30) reported the presence of greater numbers of NK cells in peritoneal fluid than in either blood or spleen. The significance of this intriguing finding is not clear, though it suggests as one possibility that the peritoneal cavity may be a site for the elective localization of NK cells. Whatever the precise status of the non-adherent NK cells, there is no doubt that in

the routine light microscope examination of peritoneal fluid cells they would be classified as lymphoid.

Transitional (Stem) Cells

Yaffe and Yoffey (6) first drew attention to the presence in the peritoneal cavity of cells with the morphology and labeling properties of transitional cells. In the bone marrow the transitional cells constitute the stem cell compartment, in which are to be found both the committed and the uncommitted stem cells (7,31,32). It should be emphasized that transitional cells have been recognized since the early days of hematology, but have been given a wide variety of names. A full discussion of the confused terminology will be found elsewhere (7,32). The question arises whether the transitional cells in the peritoneal cavity possess properties similar to those in the bone marrow. The indications are that some of them may do so.

The presence in the peritoneal cavity of the uncommitted pluripotential stem cells, the CFU-S, was first shown by Goodman (8) and Cole (33), but little attention seems to have been paid to them since then. It is clear from their data that the CFU-S are present in only small numbers. More recent work has drawn attention, in addition, to the presence of committed stem cells. Thus, Lin and Stewart (34) described the presence of CFU-C in the peritoneal cavity of the mouse. Lin (35) subsequently noted that the number of CFU-C could greatly increase after the intraperitoneal injection of thioglycollate. Stewart et al (36) made the further observation that, under appropriate culture conditions, the thioglycollate exudate cells could grow actively, and give rise mainly to macrophage colonies, as also to an occasional colony of fibroblasts.

In early work on colony-forming cells it was stated repeatedly that they could not be morphologically identified. What in fact was generally meant by this statement was that no serious effort was made to identify them. As soon as such efforts were made, it became clear that, taking into account the difficulties arising from confused terminology, the various colony-forming cells were members of the transitional cell compartment (7,31,32,37-40). Moore et al (37) specifically noted that this was the case for the CFU-C in bone marrow, where they could develop into both macrophages and granulocytes (CFU-GM), whereas the peritoneal CFU-C developed predominantly into macrophages (34,36). It would thus appear that it is mainly the macrophage line of development which occurs in the peritoneal cavity, or that the cells which enter the cavity are for the most part already committed to macrophage formation, the so-called CFU-Mac.

Further support for this view, namely that the peritoneal CFU-C are already committed to the macrophage line of development, may be found in the observation by Stewart et al(36) that the cells which give rise to macrophage colonies have already acquired the capacity to adhere, a macrophage characteristic. The occasional presence in their cultures of a fibroblast precursor recalls the earlier observation of Shelton and Rice (41) who cultured normal peritoneal cells in diffusion chambers, and found that an organized tissue developed, including fibroblasts. After two weeks collagen was identified in the chambers, both by chemical analysis and electron microscopy.

The presence in the peritoneal cavity of macrophage precursors could be interpreted as a normally occurring stage in the formation of peritoneal macrophages, but the role of the CFU-S is not so obvious. Although, from the work already quoted (8,33), the peritoneal CFU-S appear to possess full hemopoietic potential, they do not seem to undergo hemopoietic development while in the peritoneal cavity, possibly because of the lack of an appropriate stromal background. By contrast, in the adjacent omentum conditions appear to favor granulocyte formation, though not erythropoiesis (42). In murine experiments, the I.P. transfusion of large numbers of bone marrow or spleen cells may result in the development of hemopoietic colonies in the omentum (42,43) or mesentery (44).

We do not know in what numbers the CFU-S enter the normal peritoneal cavity, how long they remain there, or what happens to them if and when they leave. In early experiments on marrow transfusion

following irradiation, Congdon et al (45) compared the efficacy of three different routes of transfusion: intracardiac, intravenous, and intraperitoneal. The intracardiac route was found to be more effective than the intravenous, and the intravenous more effective than the intraperitoneal, suggesting a relatively slow exit of cells from the peritoneal cavity. However, it is difficult to institute comparisons between the fate of stem cells in normal and experimental animals. In the latter one is usually dealing with large numbers of stem cells, whereas in the former the number of stem cells is unknown.

The same kind of problem exists in relation to other connective tissues. Thus Tyler et al (46) examined the subcutaneous inflammatory exudates formed in mice after the implantation of coverslips. They observed that when the cells of these exudates were transfused into irradiated recipients, they were capable of promoting erythropoietic recovery as measured by ^{59}Fe incorporation into the spleen. The exudate cells were at least twice as effective in their repopulating ability as an equal number of blood leukocytes, and one tenth as active as bone marrow cells. The erythropoietic activity appeared to be closely associated with a mixture of cells consisting mainly of monocytes, macrophages, and cells termed 'monocytoid'. At a later date Scuderi et al (47) observed the presence of transitional cells in the exudate. More recently, in skin window exudates from normal human subjects, Sokol et al (48) have also found cells with typical transitional cell morphology.

As in the case of the peritoneal stem cells, we do not know in what numbers the hemopoietic cells enter the subcutaneous and other connective tissues, how long they remain there, or whether they gradually lose their hemopoietic potency. Micklem et al (49) suggested that many of the CFU-S in the circulation — from which presumably the peritoneal and other connective tissue stem cells are derived — undergo clonal senescence, and may in fact have been "expelled as waste products from the bone marrow." This concept of stem cell rejection by the marrow was based on the observation that there are marked differences between blood and marrow stem cells in their capacity for self renewal, and in the size of the descendant population to which they give rise under identical conditions. This view was subsequently given some support by the work of Chertkov et al (50), who agreed that circulating CFU-S did in fact have a lower capacity for self-maintenance than marrow CFU-S, but that nonetheless there were undoubtedly some high-maintenance CFU-S in the circulation. This finding suggests as one possibility that there may be a constant passage of stem cells into the circulation, and thence to the peritoneum and connective tissues generally, as well as to other parts of the lymphomyeloid complex. If this is the case, it would be reasonable to suppose that while the older cells might undergo senescence, there would also be present some recently arrived cells with as yet unimpaired high-maintenance capacity. It remains to be established how far considerations of this kind apply to the peritoneal CFU-S.

LIFE HISTORY OF PERITONEAL LYMPHOID CELLS

There are many gaps in our knowledge of the origin and fate of the peritoneal lymphoid cells. They appear to have a multiple origin.

1. Proliferation in the peritoneal cavity.

A variable but usually small amount of proliferation may occur in the peritoneal cavity. In the mouse, about 2% of the peritoneal cells normally label with thymidine, and of these about 1% are in the non-adherent group, which is predominantly lymphoid and includes a small number of transitional cells (6).

Shands and Axelrod (51) obtained similar results in the normal animal, and noted that the number of labeling cells underwent great increase after several intraperitoneal injections of tritiated thymidine. In the rat, Harris et al (52) found that about 1% of peritoneal cells were labeled after either the intravenous or the intraperitoneal injection of $^{3}HTdR$. They described most of the labeling cells as 'large mononuclears', but there were also some typical lymphocytes.

Most of the studies of the thymidine labeling of peritoneal cells have been directed to the labeling of macrophages (51,53-56). Yoffey and Yaffe (57) have recently reported a sharp rise in the labeling index of peritoneal lymphoid cells after the subcutaneous injection of thioglycollate. The subcutaneous route was chosen in order to avoid the effects of direct peritoneal irritation. Twenty-four hours after injection, the percentage of labeled cells as a whole rose from 2.1 to 11. At this time 12.8% of the lymphoid cells were labeled as against 1.73% of the macrophages. In experiments of this nature, one of the problems which arises is whether the proliferating lymphoid cells were stimulated to divide while in the peritoneal cavity, or whether the stimulus reached the cells in some extraperitoneal site, where they first entered into DNA synthesis, and then while in S migrated to the peritoneum.

2. Origin from extraperitoneal sites.

The entry of lymphoid cells into the peritoneal cavity from extraperitoneal sites raises the problem not only of their origin, but also of the channels of entry into and exit from the peritoneum. Furthermore, since there is little evidence of cell death in the peritoneal cell population, the additional question arises of the extent to which, in the normal steady state, cells are continually entering and leaving the peritoneal cavity. The size of the peritoneal cell population would thus represent a dynamic equilibrium between incoming and outgoing cells.

As far as incoming cells are concerned, the main channel of entry has been assumed to be the subserous blood capillaries, through which cells enter from the bloodstream. The increased entry of cells into the peritoneal cavity following the intraperitoneal injection of a variety of substances could be due in part to inflammatory changes in the subserous capillaries.

An unknown factor as a source of cells in the peritoneal cavity is the cell collections which have come to be known as 'milk spots'. First noted by Van Recklinghausen (58) in the omentum and the pleural subserosa, they were termed 'milk spots' (taches laiteuses) by Ranvier (59) because of their whitish appearance. Kampmeier (60) and Mixter (61) devoted special attention to the subpleural milk spots. More recently Beelen et al (62,63) performed histochemical and ultrastructural studies of the omental milk spots, which have a blood supply, and increase in number and size during peritoneal inflammation. The milk spots are present even in germ-free animals. DeBakker et al (64) observed DNA synthesis and mitosis in milk spot macrophages after peritoneal cell depletion. Lymphocytes are also present in the milk spots, but relatively little attention has been devoted to them. It seems reasonable to assume that milk spots contribute some cells to the peritoneal cavity, but whether they are a major or a minor source of peritoneal cells must for the time being be left an open question. It is also not clear to what extent they are a site of cell proliferation, or a channel of transit for cells entering the peritoneal cavity from the bloodstream.

3. Sites of origin. Primary and secondary.

The lymphoid cells which ultimately enter the peritoneal cavity can come from a variety of sources, but basically one has to distinguish between primary and secondary sites of origin. In postnatal life the bone marrow is the primary source of B lymphocytes, and the thymus of T lymphocytes, allowing for the fact that the T lymphocyte precursors are also of marrow origin. From these primary sources lymphocytes can presumably obtain ready access to the peritoneum via the bloodstream, as shown in the case of the bone marrow by transfusing a suspension of labeled marrow cells (65). Labelled lymphocytes are then found in the peritoneum after a few hours. The similarity to connective tissue elsewhere is shown by the experiments of Volkman and Gowans (66), and of Spector and Willoughby (67).

Secondary migration streams may arise in various constituents of the lymphomyeloid complex. Thus, B cells can migrate from marrow to lymph nodes, and take part in the proliferative changes when an antigen reaches the node (68). The cells so produced in the node can then migrate to enter the blood, either directly through the walls of blood vessels, or indirectly via the

lymph stream (69). From the blood they may then obtain access to the peritoneal cavity. Similar considerations apply also to the T cells which become involved in the changes occurring in the lymph node.

A short-term lymph node response, and subsequent migration of cells to the peritoneum, is illustrated by experiments such as those of Turk and Polak (70), who painted the ears of guinea-pigs with oxazolone, then labelled with tritiated thymidine the proliferating cells in the regional lymph node. Four days later, labelled lymphocytes were found in the peritoneum. Over a longer period Rosenstreich et al (71) injected antigen into the footpad of guinea-pigs, and 2-4 weeks later found many specific effector cells in the peritoneal exudate lymphocyte pool. Rosenstreich and Shevach (18) later found increased number of T lymphocytes in the exudate. It is pertinent to note that, in the normal CBA mouse, Raff (16) found 35% of T cells in the peritoneal cavity.

Koster and McGregor (72) noted that labeled thoracic duct lymphocytes, when transfused, readily entered the inflamed peritoneal cavity. However, when they transfused labelled cells from mesenteric lymph nodes, not a single labelled cell was found. Experiments of this kind raise the possibility that not all lymphocytes enter the peritoneal cavity with equal facility. There could conceivably be a mechanism for the selective entry of certain lymphocytic subgroups into the peritoneal cavity, but this is a point which requires further clarification. The pool of recirculating lymphocytes may possibly have free access to the peritoneal cavity, though in what numbers and at what rate is unknown.

4. Cell outflow

The exit of cells from the peritoneal cavity is generally assumed to be via the diaphragmatic lymphatics, if one may judge by the course taken by red cells injected intraperitoneally (73). A full discussion of the diaphragmatic lymphatic pathway will be found elsewhere (69). Cells with migratory properties, such as lymphoid cells, could conceivably leave in any part of the peritoneal cavity by migrating in any part of the cavity through its peritoneal lining. The fate of lymphoid cells which enter the subperitoneal connective tissue would presumably be the same as that of lymphocytes in connective tissue elsewhere.

It is clear from the literature that within a short space of time there can be a considerable increase in the number of cells entering and leaving the peritoneal cavity, but the diaphragmatic outflow pathway, usually ending in the right lymph duct, has not been adequately studied. Comparisons have been made between the cell populations of the thoracic and right lymph ducts (74), but the results are complicated by the not infrequent occurrence of anastomoses between these two ducts (69). Furthermore, lymph in the right duct has pulmonary and cardiac components, as well as peritoneal (75). The specific peritoneal component can only be ascertained from lymph collected close to the diaphragm.

LYMPHOID CELLS AND MACROPHAGES

Finally, in considering the heterogeneous population of peritoneal lymphoid cells, it must be noted that many observers have described the existence of cells which were interpreted as intermediate forms between lymphocytes and macrophages (1,41,53,76-81). The larger lymphoid cells have been considered the more likely macrophage precursors (79,80). However, in recent years there has been a tendency to disregard this view, and to focus attention upon the monocyte as a macrophage precursor (82), though an exclusively monocytic origin of macrophages has been disputed (83,84).

As far as a lymphoid origin of macrophages is concerned, the evidence adduced has been both morphological and functional. From a morphological point of view it is easy enough, as noted by many observers, to find a series of cells apparently intermediate in structure between typical lymphocytes and typical macrophages. It becomes difficult at times to know whether such intermediate forms should be classified as lymphocytes or macrophages. The use of

terms such as 'lymphomonocytoid cells' and 'monocytoid cells with round nucleus' (3) gives an indication of the kind of difficulty which has been encountered in arriving at a decision on the basis of morphology (cf. Daems and Brederoo, 85).

From a functional point of view, two properties generally associated with macrophages — endocytosis and adherence — have been found to be present in a certain number of cells described as lymphoid. As already noted, some lymphocytes are capable of endocytosis (3,6,20,21), but these endocytotic lymphocytes appear to persist as lymphocytes for the most part, and not to develop into macrophages.

With regard to adherence, a special group of adherent but non-phagocytic cells was described by Nathan et al (79). These cells were 'morphologically intermediate between typical macrophages and typical small lymphocytes'. They formed 6% of the adherent cells in normal mice, and 18% of the adherent cells in mice given intraperitoneal injections of BCG. These findings suggest that if in fact some lymphocytes can function as macrophage precursors, the first stage in their development into macrophages is the acquisition of the capacity to adhere. The observations of Stewart et al (36) seem to be in accord with this concept.

In view of what is now known about the various subsets of the lymphocyte population, it would not be too surprising if a specific subgroup of lymphoid cells turned out to be macrophage precursors. But whether this is actually the case or not, it would appear to be well worthwhile to establish more accurately the identity of the cells which a number of observers find it difficult to characterize as other than lymphocytes, and which they consider to be capable of differentiating into macrophages.

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