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Mesenchymal activity as a factor in resistance against mouse sarcoma in chick.

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The digestive capacity of a mesenchymal cell in the embryo and of a connective-tissue cell in the adult organism has been recorded many times in the literature.

A mesenchymal embryonic cell, being a very mobile element, will easily detach itself from the common mesenchymal syncytium, and in the presence of a foreign body will ingest it. Under normal conditions, such foreign bodies in the embryo are for the greater part red blood-corpuscles. While the vascular channels in the embryo are undergoing extensive rearrangement, erythrocytes are frequently found free amongst mesenchymal cells and ingested by the latter. Whether or not an erythrocyte undergoing ingestion is still alive, we do not know. It is a highly differentiated cell, in an unfavorable medium while outside the vessels, and with no further power of proliferation.

The ingested blood-cell undergoes within the phagocyte (of mesenchymal origin) a series of chemical changes, some of them demonstrable under the microscope, which transform it into a structureless mass of protein and result in complete digestion. The embryonic mesenchymal cell, therefore, not only is able to synthesize proteins at the expense of amino-acids, but has itself a digestive power. The intra-cellular digestive capacity of a mesenchymal phagocyte may give us a basis for the understanding of other aspects of a similar activity. Thus, chondroclasts, osteoclasts, and clasmatocytes, which are but modified mesenchymal cells, exercise a digestive power, either intracellular or extracellular.

The mesenchymal embryonic cell is capable of digesting its own proteins in the form of dead cells and possibly some living cells which have lost their normal correlations with the tissues of the organism, and it exercises this power from the earliest stages of embryonic development. We know little of its response to foreign proteins and to normal living cells. We do know, however, that it has no power over, and, therefore, no injurious effect upon, tumor cells. Tumor cells will grow amongst, and together with, mesenchymal cells.

The digestive power of adult mesenchyme (fibroblasts, clasmatocytes, splenic cellular reticulum) is much greater. We see fibroblasts and clasmatocytes ingest red blood-corpuscles after hemorrhage, and particles of a disintegrating nerve after section of a nerve trunk. Under normal conditions macrophages in the spleen are actively engaged in the phagocytosis of red blood-corpuscles. Artificially separated cells of the splenic mesenchyme may contain dozens of red and white blood-cells in their cytoplasm; or, again, fibroblasts in a culture may be seen loaded with particles of artificial medium. The ingested substances undergo an intracellular digestion.

Moreover, the adult mesenchyme of the splenic cellular reticulum, when compared with that of the embryo, is found to have acquired a new property. Embryonic splenic mesenchyme in the chick does not show any inhibiting power even as late as the hatching period, much less any destroying power over any kind of tumor cells. Tumor and splenic mesenchyme of a hatching chick thoroughly mixed will grow on the allantois well, as though transplanted independently. Splenic mesenchyme of the adult fowl, on the contrary, possesses the power of checking the Ehrlich mouse sarcoma (in its present phase of growth in the Crocker Laboratory), and in retarding the growth of the very malignant mouse sarcoma 180. The photographed preparations (demonstrated by lantern slides), show a curious relationship developing between the mesenchymal part of the adult tissue and the tumor when these are thoroughly mixed together and grafted on the allantois of a 7- or 8-day chick embryo. The tumor cells are not injured mechanically by this procedure, nor do they show any signs of an immediate injurious action by the enzymes which are known to be present in the spleen, for intensive growth of tumor mixed with spleen is observed during the first two, and sometimes three days of further incubation of the egg.

The tumor begins to grow in such grafts in the form of small foci surrounded by adult mesenchyme, the tumor cells assuming the form of polygonal or fusiform bodies in a syncytial and even plasmodial arrangement. Soon, however, in the region in which both tissues come into contact, the tumor cells, whether in mitosis or in the resting stage, become separated one by one from the syncytium. Mesenchymal cells closely encircle them and form around them a wreath of nuclei with a common cytoplasm, frequently giving the impression of large giant cells with a tumor cell within their cytoplasm. The tumor cell, at first closely surrounded, is soon found to be situated in a vacuole, the cell itself diminishing in size, gradually losing its structure, and finally completely disappearing. A graft of Ehrlich sarcoma, though showing at first an extensive growth, and in control animals reaching in 7 to 9 days a size of 1 to 1.5 cm. in diameter, is generally brought by this process to disappear five days after grafting. Not a single tumor cell could be discovered under the microscope in full series of grafts, though the identification of the large cells of the Ehrlich sarcoma amongst the chick mesenchyme is rather easy. An absolute biological proof of the destruction of the tumor cells could be obtained by the inoculation of such grafts into mice. A similar activity of the adult splenic mesenchyme, though affecting sarcoma 180, was not sufficient to check completely this very fast-growing tumor, and the tumor still grew in spite of a partial destruction easily demonstrable under the microscope.

The process of separation of the tumor cells with their subsequent death and final disappearance of digestion, takes place on the whole circumference of the tumor foci, if tumor and spleen are thoroughly mixed together. If grafted separately but adjacent to each other, the process develops only in that region in which both grafts come into contact, and not on other parts of the circumference. If the grafts be separated by a considerable space, the reaction will develop if, and at the time when, both tissues come together. This reaction, therefore, depends not upon a resistance of the host, which was supposed to be conferred by the introduction into its organism of a bit of spleen with its small lymphocytes, but upon the functional properties of the splenic mesenchyme introduced. This process is certainly not a mechanical result of intergrowth of tumors and any kind of mesenchymal tissue, for intergrowth takes place between the cells of the Ehrlich sarcoma and mesenchyme of a hatching chick with no injurious effect upon the tumor. The process depends, therefore, upon a property which the mesenchyme acquires after birth. There is a biological functional difference between the embryonic and adult splenic mesenchyme in the chick, apparent in its different response to the living tumor cell of the mouse sarcoma employed in these experiments. The functional capacity of the adult splenic mesenchyme—new in its power to injure a living tumor cell—might in my opinion be induced by factors closely connected with the great changes which take place after birth in all organs of digestion and assimilation.

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Further proof of the antagonism existing between the thymus and parathyroid.[1]

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Larvæ of the salamander *Amblystoma opacum* when fed on thymus soon after hatching develop tetanic convulsions at an age of from 35 to 40 days. Since at this time the larvæ develop, in their own thymus glands, the structures characteristic for the secretory stage of the glands, it was concluded that the amphibian thymus like that of the mammalian thymus excretes a toxic substance producing tetanic convulsions, and that tetany results if the animal's own secretion is added to that introduced by the thymus diet.

This is confirmed by further experiments (Table I., first four horizontal rows), which show that the interval between the beginning of the thymus feeding and the outbreak of tetanic convulsions becomes shorter, the later the thymus feeding is started, while the age at which tetany develops, remains constant.

If thymus feeding is started after the development of the functional stage of the animal's own thymus glands has taken

[1] *Jour. Gen. Physiol.*, 1918, i., p. 23 and 33.