On the possible role of incomplete phagocytosis in carcinogenesis and metastasis

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Abstract

Chronic inflammation is considered a major contributor to cancer genesis. Chronic inflammation is characterized by a productive tissue reaction with infiltration by mononuclear cells (macrophages, lymphocytes, and plasma cells), foci of necrosis, failure of repair, angiogenesis, and tissue sclerosis. Macrophages are the essential cells involved in chronic inflammation. Chronic inflammation begins with the accumulation of a critical number of activated macrophages in one place. The chronic inflammation can be caused by microbes or non-infectious agents however the body itself is unable to get rid of them. A number of microbes absorbed by macrophages escape destruction. They remain viable and actively multiply. That is a pattern of imperfect phagocytosis. The spread of infection is observed in lymph nodes, liver, lungs and bones. The macrophages that contain microbes become active and begin to secrete inflammatory mediators. Hypothetically, cancer cells can also cause imperfect phagocytosis and the associated chronic inflammatory reaction. The cancer cells that are trapped in the macrophages may survive due to disruption of apoptosis in them. Imperfect phagocytosis activates macrophages and the above mentioned mechanisms of chronic inflammation. In the case of imperfect phagocytosis the cancer cells that are hidden in the macrophages can move, penetrate into the lymphatic or blood vessels and easily reach lymph nodes with the aid of macrophages. Cancer cells can multiply inside the carrier macrophages. Having reached the lymph nodes the phagocytes with incubated cancer cells die, then immunization of cancer cells occurs in the lymph nodes and a new cycle starts. The sizes of microorganisms and stem cells are comparable and vary within 1 - 4 microns. Macrophages are much more active in phagocytizing microobjects 1 - 4 microns in size. Presumably, the small size of stem cancer cells could cause a special macrophage "tropism" to them. Hidden in the macrophage, cancer cells are partially or completely protected from an immune attack and they become hardly available to chemotherapy as well. Therefore, incomplete phagocytosis can serve as a serious obstacle to successful chemo- or immunotherapy. The presence of dormant or multiple cancer cells in macrophages is a predictive signal and indicates the necessity for completion of the phagocytosis.

Here we propose the scheme of carcinogenesis: The violation of apoptosis, immortalization of cancer cells - incomplete phagocytosis - chronic inflammation, remodeling of the extracellular matrix - epithelial mesenchymal transition, anoikis, production of "chimeric" exosomes -  transportation of persistent cancer cells by phagocytes - metastasis and tumor progression. Violation of non-specific mechanisms of immunity is the first phase of carcinogenesis, followed by a violation of specific mechanisms - recruitment of T helpers and killers. Macrophages represent the main “conspirators” in carcinogenesis and the deficiency of phagocytosis is a phenomenon around which the drama of carcinogenesis develops and ignoring this may prevent the goal. (TCM-GMJ April 2020; 5(1):31-P35)

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Recenty, great progress has been achieved in elucidating the mechanisms of oncogenesis and metastasis. In particular, along with different genetic and epigenetic changes and remodeling of the extracellular matrix (1,2,3,4,5,6,7,8,9,10) that play crucial role- in oncogenesis, other numerous factors have also been revealed. They are: adhesion factors (14,15), cytokines (11,12) enzymes (15), angiogenesis-stimulating factors (6), integrins (13, 14). The role of macrophages, N- killers, T-lymphocytes, T-reg cells, immunoglobulins is also well established (16,17,18,19,20,21). However, many questions still remain unclear.

Chronic inflammation (CI) is one of the most significant carcinogenic factors (22). CI also occurs under the influence of microbial or non-infectious agents, from which the body is not able to free itself (23). A number of microbes absorbed by macrophages do not break down. They remain viable and actively multiply (endocytobiosis). That is an example of imperfect phagocytosis. The spread of infection is observed in the lymph nodes, liver, lungs and bones. The macrophages containing microbes become active and begin to secrete inflammatory mediators. Penetrated from the blood monocytes gather around the activated macrophages and as a result, the so-called granuloma (mononuclear infiltrate) is formed. Activated macrophages increase the permeability of microvessels by weakening the capillary tissue barrier.

Macrophages can absorb the non-infectious particles from which the cells are unable to cleave or release them
to the environment. These metabolic products can also activate macrophages and trigger the mechanism of CI. Such pathologies include atherosclerosis, sarcoidosis, many rheumatoid and non-infectious diseases.

Can the phagocytized cancer cells activate macrophages and launch a chronic inflammatory process that is similar to the one induced by infectious agents? The question is legitimate, since the process of apoptosis in cancer cells is disrupted. With a positive answer, we will deal with something similar to “cancerous chronic infection” or “cancerous sepsis.”

The adverse effects of macrophages are found in many infectious diseases and sepsis (23, 24, 25, 26, 27, 28). Adverse effect of macrophages on progression of tumorigenesis has also been observed for a long time. They are actively involved in the inflammatory processes associated with cancer (29, 30).

It has been stated that in many types of tumors the level of the tumor-associated macrophages (TAM) infiltration is of great prognostic value. TAMs are associated with poor prognosis for cancer of different locations (31) (32, 33, 34).

The analysis of theoretical and clinical data reveals lots of similarities between the two processes: inflammatory reactions of connective tissue caused by imperfect phagocytosis (despite the etiology) and pathological changes in the extracellular matrix during oncogenesis. The latter can also be induced by an acquired deficiency of phagocytosis - imperfect phagocytosis. Although etiological factors are completely different in cancer and chronic inflammation, a similar clinical manifestation makes us think about the similarity of pathogenetic factors. The picture of chronic granulomatous disease and cancer is sometimes so similar that they require differential diagnosis to distinguish between them (by use of CT, PET, biopsy, follow-up) and it is often impossible to conduct differential diagnosis without a pathomorphological study (25, 26). (See Clinical Demonstration below. Figures 1, 2).

We have no good reason to exclude cancer cells from the factors related to imperfect phagocytosis and associated with that chronic inflammatory response. The cancer cells that are trapped in macrophages may not die, since the process of apoptosis is disrupted in them. Imperfect phagocytosis of cancer cells should activate macrophages and the above-mentioned mechanisms of chronic inflammation. It will be completely illogical to assume that the body cannot destroy cancer cells, and the fact that the body cannot destroy cancer cells, will tend to fence itself off from them, in a similar way as in chronic granulomatous inflammation. In this case, the course of the disease will also be aggravated more and there will exist a high risk for further spread of the disease.

In the mechanisms of carcinogenesis, a special role is given to the epithelial mesenchymal transition (EMT). EMT is also noted in "non-tumor" inflammations (22, 35, 36, 37). Inflammatory mediators are known to stimulate EMT (38). What is the role of imperfect phagocytosis in EMT?

Macrophage with a persistent tumor cell in it, is essentially a chimeric cell. What information does the "chimeric" exosomes developed contain? (39).

Regarding the role of CI in the epithelial mesenchymal transition one cannot avoid the epithelioid transformation of macrophages in chronic inflammation (incomplete phagocytosis) (40, 41, 42). It is theoretically acceptable and logical to expand the epithelial - mesenchymal transition scheme by adding the epithelioid transformation of macrophages to it: macrophages - transformation into epithelioid cells - epithelial mesenchymal transition (MEMT). Theoretically to exclude this is not profitable and there is a need for experimental study of this option. With confirmation of MEMT, the role of deficiency in phagocytosis observed in carcinogenesis will increase even more.

In the case of "imperfect phagocytosis", the cancer cells hidden in macrophages can move, penetrate into the lymphatic or blood vessels and freely reach the lymph nodes by means of macrophages. Cancer cells can multiply inside the transporter macrophages. Having reached the lymph node, phagocytes with incubated cancer cells in them die, insemination of the cancer cells occurs in the lymph nodes and a new cycle starts.

How realistic is the repetition of the imperfect phagocytosis scenario for cancer? The size of microorganisms varies mainly within the range of 1 to 4 mcm. Most animal cells have a diameter of 10–20 mcm. The size of macrophages is 15-80 microns (43).

Stem cells are much smaller than highly differentiated cells. It turned out that the sizes of microbes and stem cells are of the same range and comparable. Macrophages much more intensively phagocytize microobjects measuring 1-4 mcm (44).

Cytometric studies show that small cancer cells have higher associated properties (clonal, clonogenic and oncogenic abilities) typical to cancer stem cells (CSC).

Perhaps the small size of cancer stem cells explains the special “tropism” of macrophages to them. We also assume that cancer stem cells not only “fit better” into macrophages, but they also successfully reproduce there. In the framework of the “unfinished phagocytosis” model, the idea arises that in macrophages there might be selection in favor of CSCs and stimulation of their proliferation. Let’s name this process cambialization (45) (Figure 3).

The following cell populations belong to the phagocytic system: macrophages of loose fibrous connective tissue, liver vessels, macrophages of blood-forming organs (bone marrow, spleen, lymph nodes), lung macrophages, peritoneal macrophages, bone tissue osteoclasts, giant multinuclear cells of foreign bodies, glial macrophages of nerve tissue (microglia).

It is easy to notice, metastasis occurs actively in tissues and organs rich in phagocytes. The above can be explained actually by the fact that macrophages of these organs can capture and phagocytize circulating in the blood cancer cells, nuclei or their lysis derivatives, followed by incubation and insemination of cancer cells with priority for cancer stem cells. The process can occur in neighboring tis-
sues of the primary tumor as well as in regional or distant lymph nodes, mesenchymal tissues, where there are target cells - phagocytes.

Once in a macrophage, the cancer cell is partially or completely protected from an immune attack and becomes not easily available to chemotherapeutic drugs. Therefore, incomplete phagocytosis can be a serious obstacle to successful chemo- or immunotherapy. The presence of dormant or multiple cells in macrophages has a prognostic value and indicates the need to complete phagocytosis.

Using this mechanism, the relative independence of the rate of metastasis on the size of the primary tumor on the intensity of carcinema can be explained (6).

For the normal functioning of phagocytes and the successful completion of phagocytosis, oxygen is required. Cancer cells actively consume oxygen as their persistence in macrophages can cause a strong oxygen starvation of the latter. It should be noted that in cancer cells the main type of glycolysis is anaerobic (in this case, CCSs are similar to anaerobic bacteria). All these can cause a secondary deficiency of phagocytosis.

So the idea arises of using prolonged hyperbaric oxygenation in the treatment of certain forms of cancer. The effect can be enhanced in combination with chemotherapy, radiotherapy and immunotherapy.

We can conclude that cancer cells can recruiting not only T lymphocytes to inhibit antitumor immunity, but the macrophages as well.

Here we offer the following scheme of carcinogenesis, where the role of secondary phagocytosis deficiency is obvious:

Violation of apoptosis, immortalization of cancer cells - incomplete phagocytosis - chronic inflammation, remodeling of the extracellular matrix - epithelial mesenchymal transition, anoikis, production of "chimeric" exosomes - MEMP - phagocytosis and transportation of persistent cancer cells by phagocytes - metastasis, progression. Violation of non-specific mechanisms of immunity is the first phase of carcinogenesis further followed by the second phase, that is - impairment of specific mechanisms of immunity - the recruitment of T helpers and T killers.

The phenomenon of imperfect phagocytosis can change the strategy of investigation and treatment of cancer in general. Proceeding from the above we suggest to confirm or define the following: 1. High tropism of phagocytes to stem cancer cells. 2. The capability of cancer stem cells to multiply in macrophages. 3. The role of macrophages in the transport and spread of cancer cells to regional and distant lymph nodes. 6. The role of imperfect phagocytosis of cancer cells in the development of chronic inflammation in carcinogenesis, remodeling of extracellular matrix, anoikis, chimeric exosomes, MEMT. 4. Causes of incomplete phagocytosis of cancer cells. 5. Criteria for assessing the degree of imperfect phagocytosis (DIP) by the presence of cancer cells in macrophages, taking into account their number and size. 6. Identify the correlation between DIP and morphological criteria for tumor malignancy, the clinical course of the disease. 7. The ways to break the vicious circle of imperfect phagocytosis, including application of nanotechnology, taking into account the greatest tropism of phagocytes to objects (including medicines) ranging in size from 1 to 4 mm. 8. The effect of long-term general or local hyperbaric oxygenation on the functional activity of phagocytes and incomplete phagocytosis. 9. The methods of "strengthening" macrophages to encourage their ability to complete phagocytosis. For this purpose, application of tools of genetic engineering, cell therapy, chimeric macrophages and other methods. Based on the analysis, we suppose that without this any effort to strengthen T killers, regulators or normal killers will not give the desired effect.

In all likelihood, disruption of non-specific mechanisms of immunity should be considered as the first phase in cancer genesis. The imperfect phagocytosis of cancerous (stem) cells is then followed by impairment of specific mechanisms, such as the recruitment of T helpers and T killers.

In all the above listed pathological processes the macrophages play a prominent role that gives us reason to believe that the macrophages represent main participants in 'the systemic conspiracy of immunologically competent cells' and the secondary deficiency of phagocytosis is the central phenomenon around which the drama of oncogenesis develops.

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References:


Figure 3: Tumor-associated macrophages

The cancer cells turned up in the blood vessels are phagocytosed by macrophages located in different parts of the body. In consequence develop distant metastases.