Trends in Cancer Research
Vol. 11, 2016

Review

The inflammatory cancer cell: a powerful ontogenic and phylogenetic recapitulator

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ABSTRACT

Inflammation is considered to regulate tumor progression, invasion, migration and metastasis. The interstitial inflamed microenvironment in which the cancer cell develops is considered in this review as a space surrounded by a heterogeneous endothelium, made up of tumor neoendothelium, postcapillary venule endothelium, lymphatic endothelium and high endothelial venule endothelium. Through this barrier, the endothelium would exchange substrates and inflammatory mediators with the host organism. At the same time, the systemic inflammatory response associated with tumor development could be considered as an upregulation of extraembryonic functions, as those that are developed by the coelomic-amniotic and trophoblastic-yolk sac or vitelline structures. The coupling of these extraembryonic functions in the interstitial tumor space would induce a process of epithelial-mesenchymal transition leading to cancer cell proliferation, migration and metastasis. Likewise, the fundamental alterations of the systemic inflammatory response could represent a phylogenetic recapitulation of ancestral survival mechanisms, which would also explain the resistance of the cancer cell and its strong ability to survive, even in very adverse environmental situations.

KEYWORDS: cancer cell, inflammation, ontogeny, phylogeny

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CONTENTS

1. Introduction

One of the productive ways to confront the disease of cancer could be establishing a theory that includes both the large collection of data generated by laboratories and clinics [1] as well as the etiopathogenic hypothesis that nowadays supports the prophylaxis and treatment of cancer [2]. In this sense, at this point in time it seems appropriate to consider a theory based on the properties of the inflammatory response. This choice is based on the ubiquity of inflammation since it can integrate diverse mechanisms, which are associated not only with pathological conditions such as cardiovascular diseases, type 2 diabetes, obesity, neurodegenerative diseases and cancer, but also with physiological processes like reproduction, i.e. oogenesis and embryogenesis

as well as aging [3, 4]. In this context, the inflammatory response induction by human beings could represent a camouflaged expression of efficient mechanisms used during evolution and development [5].

2. The inflammatory trophic way and cancer development

Inflammation appears to regulate cell phases of malignant diseases including susceptibility, imitation, progression, dissemination, morbidity and mortality [6, 7]. Inflammation related to the initiation of cancer could be intrinsic, when induced by genetic and epigenetic changes of the transformed cell and extrinsic, that is, associated with infectious agents such as bacteria or virus, the recruited inflammatory hematopoietic cells or the activation of inflammatory resident cells, i.e. mast cells [7, 8] (Table 1).

However, tumor cells develop in a microenvironment in which intrinsic and extrinsic inflammation are coupled to promote and support tumor growth and spreading [2, 7, 9]. In this way, during the inflammatory response associated with tumor development, the nervous, immune and endocrine systems seem to lose their specific functions, that is, those characteristic of a normal organism, which maintain stability through change [10], while these systems express new protumoral functions that seem to be characterized by their trophic functions [11]. If so, these new pathological functions acquired by the nervous, immune and endocrine systems would play the main role in the successive phases of the inflammatory response associated with the start and development of new tumor tissue, and therefore, these phases could have a trophic meaning [11-13].

Thus, it could be considered that during the protumoral inflammatory response, the inflammatory nervous system, through sensitive and motor functions, including the ischemia-reperfusion phenomenon, would induce oxidative and nitrosative stress, associated with tissue hydration and tissue nutrition by diffusion. Thus a favorable environment is created so that by activating the leukocytic inflammatory response, the immune system progressively produces enzymatic stress and extra- and intra-cellular digestion. Furthermore, macrophages, mast cells and dendritic cells take advantage of the lymphatic circulation activation and migrate until reaching the lymph nodes where they activate lymphocytes. During the third phase of the inflammatory response, angiogenesis permits numerous substances, including hormones, to reach the tumoral tissue. Consequently, the substrates, hormones and growth factors needed are accumulated so that the inflammatory endocrine system can induce the development of the new tumor tissue [11, 12, 13].

3. The systemic axes of the inflammatory tumorigenic response

Inflammation is a complex process involving systemic alterations related to the stress response [14]. Back in 1936, Hans Selye described the stress response or General Adaptation Syndrome as a non-specific response to any stressor [15] and compared this syndrome to the Inflammation Syndrome [16].

However, Dvorak recognized that the composition of tumor stroma is very similar to that of the granulation tissue of healing skin wounds and suggested that “tumors are wounds that do not heal” [17]; it has been accepted that tumors are also a local process. This concept today exceedingly reduces the knowledge of both conditions, wounds and tumors, since it avoids a true comprehensive understanding of their systemic pathophysiological concept.

The systemic inflammatory response common to wounds and tumors could be made up of two overlapping phenotypes or axes, the neurogenic and the immune, which when locally overlap, facilitate the development of new normal or pathological tissue [14, 18] (Table 1). The neurogenic inflammatory phenotype begins its expression with an immediate pathological sensorial and motor response that includes an ischemia-reperfusion phenomenon with systemic and local hemodynamic impairments. A common and basic mechanism of this neurogenic response would be sudden hydroelectrolytic alterations with abnormal ion transport, edema and activation of the lymphatic circulation [19, 20]. Consequently, mediators of the neurogenic stress response including substances produced by the hypothalamic-pituitary-adrenocortical, sympathetic-adrenal medullary and renin-angiotensin-aldosterone axes, are selectively accumulated in the interstitial space of the tissue

Table 1. Different characteristics of the inflammatory cancer-related response.

Mechanisms of tumor initiation and development				
	Inflammation-related with cancer initiation	Inflammatory trophic systems	Inflammatory stress responses axes	Re-expression of extra-embryonic functions
Inflammation and cancer	* Intrinsic - genetic - epigenetic * Extrinsic - Infectious agents · bacteria · virus - Inflammatory cells · Bone marrow origin · Resident in tissues	* Nervous - Ischemia-reperfusion - Oxidative and nitrosative stress - Tissue hydration - Nutrition by diffusion * Immune - Leucocyte infiltration - Enzymatic stress - Fermentation - Phagocytosis * Endocrine - Angiogenesis - Vascular nutrition	* Neurogenic - Hydroelectrolytic alterations - Interstitial accumulation of neurogenic stress response substances · Catecholamines * Immune Interstitial storage of: - Cholesterol-derived hormones . gluco- and mineralocorticoids · estrogen · progesterone - Positive acute phase proteins · coagulation-fibrinolysis system · transport proteins · protease inhibitors - Bone marrow stem cells	* Coelomic-amniotic axis - Neurogenic potential - Interstitial edema - Cytokines and growth factors - Bacteriostasis - Anti-inflammation * Vitelline axis - Digestive functions - Lipid and protein nutrients - Acute phase proteins - Hematopoietic cell derived control - Angiogenic switch

suffering from ischemia-reperfusion because postcapillary venule endothelium permeability is increased [11, 12, 14].

The immune inflammatory phenotype could be considered both a key and complementary arm of the stress response [21]. The activation of this systemic axis contributes both molecules and cells to the inflammatory interstitial space. The molecules such as lipids, i.e. cholesterol-derived hormones, including, aldosterone, corticoids, progesterone, androgens and estrogens, predominate [22]. But, an array of other molecules, including the positive acute phase proteins, like proteins of the coagulation-fibrinolysis system (fibrinogen, prothrombin, factor VIII, von-Willebrand factors, complement factors, plasminogen), protease inhibitors (alpha-1-antitrypsin, alpha-1-antichymotrypsin), transport proteins (ceruloplasmin, hemopexin, haptoglobin) and lipid transport proteins (serum amyloid A and serum amyloid P) are involved in this immune inflammatory response [23, 24]. The cells that reach the inflamed interstitium are derived from the inflammatory activation of the bone marrow stem cell niche, which indicate the stimulation of the hematopoietic stem cells (HSCs) and the mesenchymal stem cells (MSCs), both multipotent stem cells [25]. The molecular and cellular contribution of the above-mentioned neurogenic and immune inflammatory axes to the interstitial space of the damaged tissues and/or organs, would condition the evolution/development of the newly formed tissue, whether normal or pathological [14, 21].

4. The inflammatory protumoral systemic axes: recapitulation of extra-embryonic functions

The interstitium is considered as the space where the battle of inflammation develops. During the inflammatory response, the interstitial space increases its size exceedingly as a consequence of the successive infiltration it suffers by molecules, cells and even by bacteria or its by-products [14, 21]. Since these molecular, cellular and bacterial inflammatory mediators enter the interstitium through a heterogeneous endothelial pathway, the interstitial inflammatory space could be imagined like a sphere surrounded by an endothelial barrier with multiple functions, both incretory and excretory. In the figurative sense, the inflamed area could be similar to an “endothelial egg” [14]. Thus, this inflammatory endothelial egg would receive molecules and cells originating from the activation of the systemic inflammatory axes (neurogenic and immune) through the postcapillary venule endothelium, the neovasculature formed by the tumor, the high endothelial venule in the lymph nodes and, in lesser degree, through the capillary endothelium. At the same time, the lymphatic and the tumoral neovasculature endothelium could be equivalent to an excretory system of the proposed endothelial inflammatory egg (Figure 1).

It has been previously proposed that the inflammatory response associated with the wound healing process could recapitulate ontogeny through the re-expression of two hypothetical embryonic tropic axes, that is, exocoelomic-amniotic and trophoblastic-yolk sac or vitelline, in the interstitial space of the injured tissue [14]. If so, inflammation could represent the re-expression, along the adult life cycle of ancestral mechanisms that were used for normal embryonic development [14, 21].

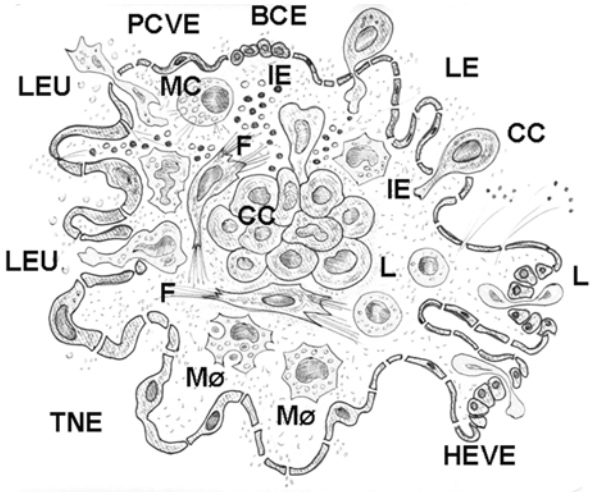

Figure 1. Schematic representation of a tumor as an “endothelial egg”. The endothelial cells surround an interstitial space where the tumor cells develop by inflammatory mechanisms. BCE: Blood capillary endothelium; CC: Cancer cell; F: Fibroblast; HEVE: High endothelial venule endothelium; IE: Interstitial edema with lipoproteins and acute phase proteins; L: Lymphocyte; LE: Lymphatic endothelium; LEU: Leukocyte; MC: Mast cell; MØ: Macrophage; PCVE: Postcapillary venous endothelium; TNE: tumoral neoendothelium.

Today, it has become clear that cancer cells also possess a more embryonic phenotype than those of the tissues where they originate, and this involves the re-expression of embryonic genes [18, 26, 27]. Both embryos and tumors display similar antigens, produce angiogenic growth factors and subvert apoptotic cell death. Furthermore, they may both avoid immune aggression by similar mechanisms [26]. If we consider the generic representation of the inflamed tumor tissue as an "endothelial egg", several hypothetical phylogenic proposals could be considered during this tumor egg development. Thanks to the influx of mediators from the activation of systemic inflammatory axes, the "endothelial egg" has different types of evolution that could range between its development with "hitching" and its defective development due to noxious factors.

The contribution by both systemic inflammatory axes, neurogenic and immune, to tumor development could be compared to the molecular and cellular contribution made by the extraembryonic tissues to the embryo. The contribution of the extraembryonic tissues that surround the embryo/fetus i.e. trophoblast, exocoelom, amnion and yolk sac [28] to the interstitial space located inside them, namely the intraembryonic mesoderm, is essential for organogenesis [29]. All of these extraembryonic tissues could be considered like two functional axes, i.e, the coelomic-amniotic axis and the trophoblastic-yolk sac, also named vitelline axis [14]. Therefore, during the protumoral inflammatory response, the neurogenic inflammatory axis could have similar functions to the coelomic-amniotic axis, and the immune inflammatory axis would represent the trophoblastic-yolk sac or vitelline axis. Also, the contribution of these two inflammatory axes is essential for tumorigenesis (Table 1).

The hypothetical recapitulation of these extraembryonic functions during the tumor inflammatory response would first express functions similar to the extraembryonic coelom that surrounds the blastocyst. Accordingly, this phenotype could be adopted by the inflamed tumor interstitium [30, 31] that subsequently induces the accumulation of fluid with characteristics similar to coelomic fluid [32] in an environment with low pH and oxygen [30, 31]. In essence, interstitial edema with high levels of electrolytes, metals, amino acids, cytokines, proteins and antioxidants [32-35] would be produced in the inflammatory infiltrate associated with many solid tumors. This initial interstitial pro-inflammatory edema would then play the leading role in the tumor trophism, and therefore constitute a tumorigenic microenvironment.

At the same time, the recapitulation of the amniotic functions could correspond to the procurement of a strong neural potential [36] associated with the production of a combination of cytokines and growth factors which establishes a connection between mesenchymal and epithelial cells during embryo development [37]. The amniotic-like or tumor-initiating cells [38] create a hypoxic and hydrated interstitial axis [39] with cytokines and growth factors [37] favoring not only nutrition by diffusion, but also transport, excretion and bacteriostatic and anti-inflammatory protection [40] (Figure 2).

The re-expression of the trophoblastic-yolk sac or vitelline axis, would favor the development by cancer cells of aggressive traits, such as invasiveness

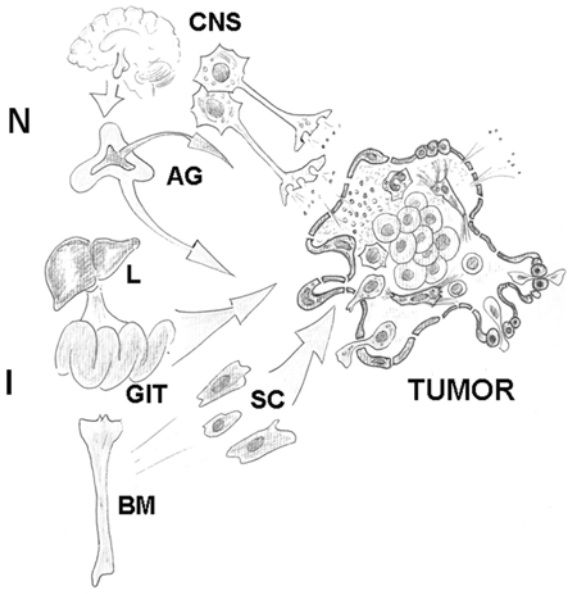

Figure 2. Relationship between the hypothesized neurogenic and immune systemic host axes and tumor development. Both axes could have functions similar to the functions expressed by the extra-embryonic membranes during embryo development. The neurogenic axis (N) could be equivalent to the coelomic-amniotic functions and in turn the immune axis (I) could represent the trophoblastic-yolk-sac or vitelline functions. AG: adrenal gland; BM: bone marrow; CNS: Central Nervous System; GIT: Gastrointestinal tract; L: Liver; SC: Stem Cells.

and metastatic dissemination [41, 42]. During trophoblast differentiation, the tumor also exhibit intense phagocytic activity, represented by the recruited tumor-associated macrophages [6, 43]. This macrophage subtype leads to events as diverse as engulfment and destruction of extracellular materials and the production of inflammatory mediators that might modulate both the immune response [44] and the tumor invasiveness [45, 46].

A major function of the yolk sac phenotype could be carbohydrate, protein and lipid accumulation for cancer cell nutrition (vitellum) [47]. The yolk-sac-related functions therefore could provide cancer cells with lipids and lipid-soluble nutrients during the early phases of development [48]. In addition, the endodermal layer of the yolk sac is the source of several proteins including acute phase proteins such as prealbumin, transferrin and α_1-antitrypsin as well as α-fetoprotein [40]. Through the induction of the synthesis and release of acute phase proteins, tumors can reduce oxidative, nitrosative and enzymatic stress [23, 49], activate the complement-coagulation-fibrinolysis system and regulate the lipid metabolism [23, 24]. Moreover, the acute phase response improves phagocytosis [24], a specific form of endocytosis primarily associated with nutrition in unicellular organisms and with innate and adaptive immunity in mammals [44]. In this sense, the yolk-sac endoderm function is considered as a digestive system in early development [48]. The recapitulated yolk sac-related phenotype could also favor the regulation of lipid metabolism genes [48]. This phenotype, also named vitelline, induces a hematopoietic-cell derived control with recruitment of immune cells and an angiogenic switch. Then, angiogenesis regulates the vascular integrity [48, 50] to enable new tissue immunological tolerance during the tumor inflammatory response (Figure 2).

The hypothesized re-expression of these extra-embryonic functional axes, namely the coelomic-amniotic and trophoblastic-yolk sac, could contribute in establishing a tumor-promoting environment and therefore be responsible for tumor initiation and progression. In this way, both axes may act on the inflamed tumor interstitium in a similar manner as they act during embryonic development. However, by using similar mechanisms an embryo is not created but the tumor tissue could be developed [26, 27, 51]. The representation of the inflamed interstitial tumor tissue as a space/area whose surface is covered by a heterogeneous endothelium could allow for a better comparative understanding between a tumor and the embryonic development (Figures 1 and 2).

5. Interstitial coupling of the inflammatory tumorigenic axes

The tumor-related inflammatory response could be considered as a complex process involving systemic alterations related to a stress response. However, the magnitude of this systemic response could range between a subclinical degree, in which case the tumor process is classified as local or regional, and cancer cachexia. This latter degree is a multi-factorial syndrome characterized by chronic wasting involving loss of both adipose tissue and lean body mass with a systemic inflammatory response syndrome (SIRS), an intense acute phase response, hypermetabolism and hypercatabolism. Such variation may be, in part, due to the patient's genotype rather than to tumor phenotype and/or tumor interaction [52].

In this review we have tried to establish similarities between the complex pathophysiological mechanisms developed during tumorigenesis and the pluripotential extra-embryonic pathways during embryo development. Therefore, based on this hypothesis, during the evolution of the tumorigenic inflammatory response, the re-expressed systemic extra-embryonic functions by the tumoral tissue condition the severity of the systemic involvement. We think that the recapitulation of the extraembryonic coelomic and amniotic functions could be represented by the early activation of the systemic neurogenic axis. In turn, the subsequent recapitulation of the trophoblast and yolk sac functions would be carried out mainly by activating a systemic bone-marrow-related axis (Figure 3).

The pathological activation of these systemic axes, neurogenic and bone-marrow-related, would focus their functions in the tumoral tissue in two steps. First, the upregulated coelomic-amniotic phenotype induces a neurogenic response with hydroelectrolytic alterations. In this early response, cells from medulla suprarenal and mast cells produce substances for export. Firstly, these cells

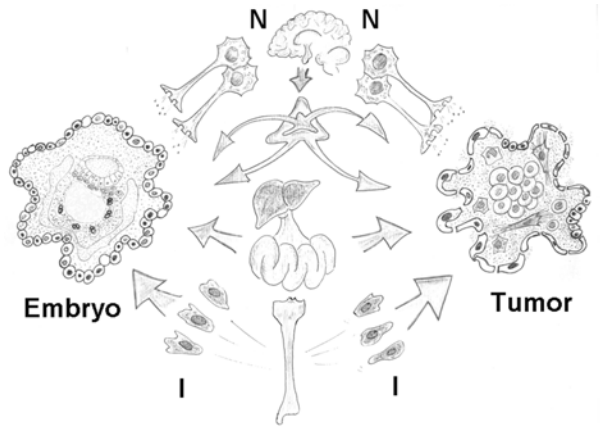

Figure 3. Comparison of embryonic development (left) and tumor development (right). The growth of both types of development would be regulated by two systemic axes, termed coelomic-amniotic or neurogenic (N) and trophoblastic-yolk sac or immune (I) since it is considered that they represent the up-regulated extraembryonic functions.

synthesize and then store large amounts of molecules, such as biogenic amines [21] in secretory vesicles ready for rapid release [8, 53]. In turn, the up-regulated systemic vitelline phenotype, represented by the inflammatory bone marrow response, produces a lipid metabolic switch linked to steroid and acute phase protein synthesis [14, 21]. This slower response developed by steroidogenic cells includes the synthesis of new steroids such as cortisol, aldosterone, progesterone and estrogen [21]. In particular, the sex steroid hormone estrogen exhibits a broad spectrum of physiological functions ranging from regulation of the menstrual cycle and reproduction to modulation of brain functions, cholesterol mobilization and carcinogenesis [54]. In addition, the increase of the acute-phase protein synthesis by hepatocytes is linked with the up-regulation of pro-inflammatory cytokines and chemokines [23, 24, 55].

Finally, both the extra-embryonic recapitulated phenotypes are coupled in the interstitium of the tumoral tissue. This interstitial integration of both pathological axes could finally induce a gastrulation-like process [56]. Gastrulation, which involves the "*de novo*" formation of normal as well as pathological tissues, is based on the recapitulation of the intra-embryonic mesenchyme formation process [29]. During development, the first instance of epithelial-mesenchymal transition (EMT) occurs during gastrulation, giving rise to the primary mesenchyme and is well-defined. However, the EMT associated with cancer and fibrosis is less clearly defined and specific to each pathology [27, 57]. A closely related phenotypic conversion is detected in cancer and is associated with the capacity of tumor cells to invade and metastasize [57, 58].

Furthermore, fibroblasts are a type of mesodermal-derived cells and they are one of the most abundant cell types found in the microenvironment of solid tumors. Cancer-associated fibroblasts can contribute to tumor growth and spread by releasing an array of growth factors and chemokines [59].

One of the main objectives of the up-regulated extra-embryonic phenotypes is the establishment of an open circulation in the tumor tissue to favor the exchange of substrates and inflammatory mediators with the host. Therefore, the neovasculature formed by the tumor is tortuous and leaky [60]. This tumor open circulatory system facilitates interstitial fluid diffusion and subsequently its own nutrition. Animals have adapted their circulatory system during phylogeny. Vertebrates have a closed circulatory system [61] whereas in invertebrates, like insects, the body fluid, that is, hemolymph, is pumped through the tissues with no closed vessels [62]. That is why it could be suspected that in the tumor, the circulatory system acquires some of the characteristics of the open circulatory system. Also, the fluid infiltrating the tumor interstitial space could become similar to the hemolymph of insects. Consequently, extravasation of plasma and blood cells is produced through this acquired open microcirculatory tumor system. Perhaps, through the up-regulation of ancestral phylogenetic mechanisms, the plasma, the interstitial tumor fluid and lymph compartments could become closely linked during tumor development, thus favoring the continuous flow of fluid and cells from one compartment to the next [21].

At the same time, one of the main phylogenetic features in the up-regulation of the vitelline phenotype consists in the interstitial accumulation of yolk material, especially cholesterol. Vertebrate

cells contain cholesterol, and although different tissues have specific patterns of cholesterol metabolism, the basic pattern is similar in all cells [63]. Today, it is accepted that inflammation and the concomitant acute phase response induce marked changes in the lipoprotein profile [64] and cholesterol metabolism [65]. In this sense, the properties of the inflammatory acute phase response and the related cholesterol traffic have been compared with the accumulation of yolk materials into oocytes during oogenesis and their mobilization during embryogenesis [5]. Cholesterol could be used locally to synthesize glucocorticoids and mineralocorticoids, which could regulate microcirculatory functions and immune cell activation [66]. In particular, the pro-inflammatory and anti-inflammatory functions of androgens and estrogens and progesterone suggest that endogenous sex steroids may influence immune functions [67, 68]. Progesterone, for example, increases vascular permeability and local accumulation of inflammatory cells [67]. In turn, a pro-inflammatory milieu can also directly increase estrogen production [69] and subsequently, estrogens could induce growth mechanisms of normal as well as malignant cells [70]. In addition, leukocytes in the inflamed interstitium could develop neuroendocrine functions, with pro-opiomelanocortin (POMC)-derived peptide production [71].

Therefore, we can hypothesize that cancer is the result of a specific type of inflammatory response during which ontogenic and phylogenetic mechanisms are re-expressed. The recapitulation of ontogenic and phylogenetic mechanisms during the inflammatory response in mammals is an old hypothesis dating back to the 19th century when Metchnikoff described macrophage function. In particular, this author recognized a long phylogenetic and ontogenic history of the phagocytes. In fact, he suggested that the phagocyte functions were the same throughout evolution, but the context has changed or was different [72].

Likewise, the relationship between the inflammatory response and cancer could be based on orchestrating ontogenic and phylogenic recapitulated systemic functions. Inflammation gives cancer a systemic pattern and this fact provides a new diagnostic and therapeutic perspective to this serious pathology. Thus, ontogenic recapitulation induced by the cancer cell would enable in steering early diagnosis and treatment of the disease, in order to modulate the mechanisms of the extra-embryonic recapitulated functions. Also, the mediators of this systemic oncological response would be similar to the mediators that drive the gestation of a new eukaryotic organism.

Finally, the involvement of survival ancestral mechanisms exceedingly broaden the etiopathological concept of cancer, since it probably means the recapitulation of cellular functions involved in the early evolution of the eukaryotic cell. If so, these ancestral mechanisms would provide to the tumor cells a strong capacity to survive in an array of adverse microenvironments.

6. Conclusion

In summary, tumor progression, invasion, migration and metastasis are closely linked to the interstitial inflamed microenvironment in which the cancer cell develops. The early tumor development occurs within a heterogeneous endothelium, made up of tumor neoendothelium, postcapillary venule endothelium, lymphatic endothelium and high endothelial venule endothelium. Through this tumor endothelial barrier, the systemic inflammatory response associated to tumor development is considered made up by two re-expressed ontogenic axes. Both axes, coelomic-amniotic and trophoblastic-vitelline ones, are coupled in the interstitial tumor space leading to cancer cell proliferation, migration and metastasis. Likewise, the cancer systemic inflammatory response could also represent a phylogenetic recapitulation of ancestral survival mechanisms, which would also explain the resistance of the cancer cell and its strong ability to survive, even in very adverse environmental situations.

7. Acknowledgements

We would like to express our gratitude to Maria-Elena Vicente for preparing the manuscript, Elizabeth Mascola for translating it into English and also to Maria-José Valdemoro, Head of Processes and Specialized Information of the Complutense University Medical School Library.

8. Conflict of interest statement

The authors declare that there aren't any conflicts of interest.

9. Abbreviations

EMT, epithelial-mesenchymal transition; HSCs, hematopoietic stem cells; MSCs, mesenchymal stem cells; POMC, pro-opiomelanocortin; SIRS, systemic inflammatory response syndrome.

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