Cancer is one of the most fatal diseases in the world. It caused almost 12% of all deaths in women and 14% in men in 2004, only next to cardiovascular diseases, infectious and parasitic diseases. After a century of combat against cancer, the outcome of cancer treatment has noticeably improved. For example, early detection, diagnosis and treatment of cancer of the cervix and breast have lead to a high cure rate for these cancer patients in the early stage of the disease. In the past decade, the progress in innovation in radiotherapy equipment and the discovery of targeted chemotherapeutic drugs have noticeably improved the survival rate for certain types of cancer at the early or middle stages, such as some gastric, colorectal, nasopharyngeal, esophageal cancers and some histopathological types of malignant lymphoma. However, in spite of these achievements, the overall survival rate for cancer, particularly regarding hepatic cancer, pancreatic and small cell lung cancer and others has still not significantly increased. Therefore, we have to pay serious attention to the basic concepts of cancer biology, especially the mechanism of carcinogenesis, cancer development and its progression, to achieve the goal of 3P cancer medicine: the prevention (primary and secondary); the prediction of cancer as well as its clinical outcome, particularly metastasis; and the personalized treatment of cancer.
1.1 Cancer is a Well-Organized Tissue, Constructing a Specified Cancer Microenvironment

Cancer is a well-organized tissue from a defined organ or tissue. It is composed of cancer cells, fibroblasts, vasculature cells, immune cells and stroma. All these components in the cancer tissue construct a specified milieu defined as a cancer microenvironment. Cancer cells are usually arranged in a nest or as cluster-like structures separated by stroma, capillary or blood vessels and stromal cells described above. Among stromal cells, the fibroblast is an important component, which may be derived directly from cancer cells via epithelial-mesenchymal-transition (EMT), or may be a non-malignant fibroblast but activated in molecular pathways and different from normal fibroblast. In recent years, fibroblasts in cancer tissues have been designated as cancer-associated or cancer-activated fibroblasts. In addition to the fibroblasts, vascular structures and angiogenesis have been described in a tremendous number of reports. Furthermore, the significance of the clinical outcome relevant to the presence of some specified identities of immune cells, including dentritic cells, macrophages and inflammatory cells has been addressed in recent years [2-4]. Therefore, we have emphasized that cancer is a specified tissue, not a cluster of cancer cells.

1.1.1 Cancer Associated Stromal Cells

Accompanying a tumor from the initial stages, cancer-associated fibroblasts (CAFs) produce abundant extracellular matrix (ECM), hepatic growth factor (HGF), transforming growth factor β (TGF-β) and other secretory proteins and lipids to accelerate tumor growth. As a tumor develops, CAFs are undergoing a series of phenotypic and biochemical changes. First, the CAFs at the interface of the tumor-stroma are markedly more abundant than the fibroblast in normal tissues [5, 6]. Second, the CAFs cultured in vitro bear a different growth pattern and morphology [5-7]. Third, CAFs are characterized by the expression of the marker proteins, such as α-smooth-muscle actin (α-SMA), fibroblast-activated protein (FAP), fibroblast-specific protein-1 (FSP1/S100A4), neuron-glial antigen-2 (NG2) and platelet derived growth factor β (PDGF β) receptor. Recent studies have identified two major subsets of CAFs on the basis of the differential expression of these marker proteins. “One subset is FSP1 positive, but lacked expression of NG2, α-SMA and PDGF, whereas the other FSP1-negative subtype co-expressed NG2, α-SMA and PDGF β-receptor” [8, 9]. CAFs can still retain these properties when they are cultured alone in vitro, even after ten population doublings [10]. An open question arises from these observations: do CAFs as well as tumor cells acquire genetic and epigenetic alterations? Publications from different laboratories have demonstrated consistent epigenetic alterations, such as DNA methylation in CAFs of breast and prostate cancer [11, 12]. However, many studies come out with
conflicting results regarding the genetic alterations in stromal cells. On the one hand, genetic alteration, including p53 mutation, is a common event in stromal cells of breast cancer and head-and-neck cancer \[13, 14\]. On the other hand, genetic alteration is extremely rare in some carcinomas in other reports \[15, 16\]. More interestingly, some other recent studies as well as our unpublished data show that genetic modification of fibroblasts can induce malignant transformation or overgrowth of naturally immortalized human epithelial cell lines. Conditional knock-out of TGF-β type II receptors in mouse fibroblasts resulted in intraepithelial neoplasia in the prostate and invasive squamous cell carcinoma of the forestomach \[17\]. Activation of paracrine HGF signaling in TGF-β knock-out fibroblasts is one possible mechanism for stimulation of epithelial proliferation.

Another puzzle of CAFs is about their origin. There are several possible sources of these cells: local fibroblasts or fibroblast precursors stimulated by members of the PDGF or TGF-β family; bone-marrow-derived stromal cells or endothelial cells, etc. It has also been suggested that CAFs are derived from malignant epithelial cells undergoing epithelial-mesenchymal transition \[18, 19\]. Nevertheless, some reports provided the opposite evidence that CAFs often fail to exhibit karyotypic alterations and are nontumorigenic \[10\].

In a broad sense, cancer-associated stromal cells also include multiple types of immune cells, vascular and lymphatic endothelial cells, which are recruited or activated by the chemokines and cytokines secreted by tumor cells to promote tumor angiogenesis and metastasis \[20, 21\]. Since Folkman firstly proposed in 1971 that tumor growth and metastasis are angiogenesis-dependent \[22\], pathological angiogenesis has been widely acknowledged as a hallmark of cancer \[23\]. During metastasis, once the disseminated cancer cell has reached its target organ, the neovascularization is required for the establishment of the metastatic lesion. The role of immune cells in tumor development is described as “corrupt policemen” \[24\]. Instead of impeding tumor growth, these immune cells engage in promoting tumor progression by providing abundant proangiogenic factors for tumor angiogenesis and metastasis \[25, 26\]. Furthermore, “tumor associated macrophages secreted proteases (MMP9) for the liberation of matrix-sequestered growth factors and for the degradation of ECM and the basement membrane, thus promoting sprouting and expansion of the vasculature and invasive motility of tumor cells” \[24\].

Moreover, the promotional role of tumor associated stromal cells in tumor growth has been well established, but stromal cells can also inhibit tumor growth by secreting and remodeling ECM proteins \[27\]. Thrombospondin-1 (TSP-1), endostatin and angiostatin are all endogenous inhibitors of angiogenesis, expressed or processed in the tumor microenvironment by stromal fibroblasts and immune cells. Desmoplasia, one common phenomenon of tumor development, appears in relatively early-stage lesions and disappears in a highly invasive, advanced tumor, which could be one of the host defense reactions designed to confine the developing tumor by tumor associated stromal cells \[28, 29\]. Desmoplasia is defined as the growth of fibrous or connective tissue, while the underlying mechanism of its formation is actually caused by the over-expression and abnormal remodeling of ECM.
1.1.2 Extracellular Matrix in Tumor

ECM is a fundamental component of a tumor microenvironment, much more than a structural support in a tumor microenvironment as appreciated previously. The structure and composition of ECM undergo dramatic alterations at the initial stage of cancer, or even before carcinogenic lesions appear \(^{30}\), and are supposed to provide suitable “soil” (microenvironment) for “seed” (tumor cells) growth. Abnormal expression and processing of ECM are common characteristics of tumors, indicating the important role of ECM in a tumor microenvironment. Both positive and negative roles of ECM in tumor development, promoting or impeding angiogenesis or metastasis, have attracted much attention of researchers in past decades. The underlying mechanisms of how ECM affects a tumor microenvironment have been elucidated in various contexts. As organized, solid-phase ligands for integrin and non-integrin receptors, ECM proteins can transduce or receive complex, multivalent signals in a spatial and temporal pattern, triggering multiple outside-in or inside-out signaling to regulate tumor behavior. As soluble, diffusible ligands, the processed or degraded small ECM fragments, named as “matrikeins” \(^{31, 32}\), could influence a tumor’s biological behavior as cytokines and growth factors. It has long been considered that ECM acts as a sink or reservoir of growth factors, which can be released during physiological or pathological conditions, for example during tumor progression. The specific, direct binding of growth factors to ECM proteins has been shown in plenty of studies. For instance, fibroblast growth factors (FGFs) and vascular endothelial growth factors (VEGFs) have a high affinity to heparin and heparin sulfate, a component of many ECM proteoglycans \(^{33}\). Furthermore, many macromolecular ECM proteins, like laminins, tenscins, etc., containing multiple EGF-like domains, can bind to EGF receptors and modulate its signaling. More strikingly, a new mechanism on how a matrix affects tumor progression has recently been proposed so that the level and nature of ECM crosslinks in a tissue could impact cancer risk and alter tumor behavior \(^{34}\). These data could explain the dramatic increase in tumor incidence with aging, which is due to the stiffer and higher level of aberrant collagen crosslinks in aged tissues.

Supported by plenty of evidence, the importance of the dynamic and reciprocal interactions between the tumor and the neighboring microenvironment in tumor development is no longer disputed. However, to date, the tumor microenvironment is still ignored in studies based on the conventional “cancer cell only” 2D culture system. 3D cancer-stromal cell co-culture models are being developed by many laboratories that better reflect the physiological environment of the tumors \(^{35, 36}\). Therefore, it could be an ideal way to unveil the mysteries of the tumor microenvironment by combining an \textit{in vitro} 3D multiple cell co-culture system and an \textit{in vivo} genetically engineered mouse model with over-expressing specific factors or conditionally knocked-out specific genes in stromal cells. With the concept of the tumor microenvironment, a new exciting strategy for cancer treatments targeting the constituents in the tumor microenvironment has been
Cancer is a Well-Organized Tissue, Constructing a Specified Cancer Microenvironment

Many bench studies, even clinical trials, have shown the promise of anti-angiogenic and anti-inflammatory therapies for cancer prevention and treatment. Bevacizumab, a monoclonal antibody against VEGF-A has demonstrated significant efficacy in various human malignancies. In the case of hepatocellular carcinoma (HCC), the components of cancer tissue remain unclear. This is, in part, due to the complex structure of normal parenchymatous liver tissue and also the unclarified cellular structures of HCC tissue. For example, the stellate cells are very important cell components in normal liver. In mouse liver, it is suggested that stellate cells may be derived from neural crest cells with expression of some neural cell markers, such as glial fibrillary protein, synaptophysin, etc.. Meanwhile, the stellate cells are also recognized as myofibrast with the contractile capability to regulate the sinusoidal blood flow in liver. However, little information is available for the role of stellate cells in hepatocarcinogenesis and cancer progression of both mouse and human origins, which will be discussed in the following section.

1.1.3 Tumor Acidic Microenvironment

Tumors have an acidic microenvironment due to their marked rate of metabolic acid production (lactic and carbonic acids) via glycolysis. The low extracellular pH (pHe) in the range of 5.6 to 6.8 and the neutral/alkaline intracellular pH (pHi) in the range of 7.2 to 7.5 are hallmarks of cancer cells. The tumor acidic microenvironment (TAM) plays an important role in cancer development, progression and metastasis. TAM can induce the selection of tumor cells to survive in this acidic condition and contribute to the transformation from benign cells to malignant cells. Acidification of the tumor extracellular microenvironment promotes metastasis and it is proposed that the extracellular acidification results in normal cell death and extracellular matrix (ECM) degradation to allow for the advancing acid-adapted tumor cells to proliferate. The low pH of the tumor extracellular microenvironment can induce increased secretion and activation of proteases and promote the degradation and remodeling of ECM through proteolytic enzyme activation, thus contributing to cancer invasion and metastasis.

Throughout the entire process of cancer metastasis, degradation and remodeling of ECM almost exist at each step. Therefore, blocking of ECM degradation has been become a prospective approach in the development of treatment for cancer metastasis. However, the results of previous trials targeting only one or several matrix metalloproteinases (MMPs) by MMP inhibitors (MPIs) are not as encouraging as expected. It should be the main reason for trial failure that the MMP family consists of over 20 members and there is no MPI (endogenous or exogenous) possession effect for all these MMP members.

Vacuolar H⁺-ATPase (V-ATPase), as a specific proton pump of the cell, is the key regulator of the tumor acidic microenvironment and has an important role in the control of pHe and pHi. We found that the inhibition of the V-ATPase function...
via knockdown of ATP6L expression using RNAi technology could effectively suppress cancer metastasis by the decrease in proton extrusion and the down-regulation of gelatinase activity \[50\]. Our data and other reports \[47, 51\] indicate that it is possible that cancer metastasis can be inhibited by raising the pH of the acidic extracellular microenvironment of metastatic cancer cells to totally suppress the activities of all proteases and to block the process of degradation and remodeling of ECM.

### 1.2 Heterogeneity of Cancer Cell Population and Cancer Stem Cell Hypothesis

Cancer cells are a heterogeneous cell population which may vary to a great extent in terms of cell morphology, molecular profiles and biological characteristics, such as the capacity of cell proliferation, tumorigenicity, drug or radiation resistance, potential for invasion, and metastasis. The cancer stem cell concept was firstly addressed in a human hematopoietic tumor in 1994 by Dick J E et al. \[52\]. Since then, cancer stem cell hypothesis for solid tumors has been addressed by Reya T et al. in 2001 \[53\]. In recent years, cancer stem-like cells have been identified in many types of cancers, including malignant glioma, cancer of the breast, colon, pancreas, liver and other tissue origin \[54-65\]. In this section, the evidence to support this hypothesis and arguments to challenge it will be briefly discussed.

#### 1.2.1 Cancer Stem Cell Hypothesis

In the last century, tumor stem cell hypothesis was addressed in acute myeloid leukemia to interpret the process of malignant myelogenic cell development and progression. For a solid tumor, the hypothesis is defined by the following essential features:

(i) Cancer is initiated by transformation of tissue stem cells, designated as tumor or cancer initiating cells or cancer stem cells.

(ii) Cancer stem cells are characterized by the following criteria: (a) Defined cell surface markers are present, which distinguishes cancer stem cells from counterparts; (b) Cancer stem cells comprise usually only a small subset among the overall cancer cell population, usually about less than 1%-5%, in some exceptional cases up to 20% or even more; (c) High self-renewal capacity is demonstrated by colony formation in a soft agar or matrigel medium; (d) High tumorigenicity of human cancer stem cells is demonstrated in nude mice xenograft. Usually, as few as several hundred cells can give rise to a tumor, in contrast to the requirement of $10^6$ cancer non-stem cells in tumorigenicity; (e) Relative resistance to drug or radiation is revealed in cancer stem cells as compared to the non-stem cancer cell population.
1.2 Heterogeneity of Cancer Cell Population and Cancer Stem Cell Hypothesis

The hypothesis seems intriguing and promising to provide an important insight into search or cancer stem cell-targeted therapy to eradicate cancer. The stem or stem-like cells from hepatocellular carcinoma will be presented in detail in an independent chapter (Chapter 7).

1.2.2 Arguments against Cancer Stem Cell Hypothesis

Though many reports were documented about the identification of cancer stem or stem-like cells in cancer from different tissue origins, cancer stem cell hypothesis is still under challenge. The major issues are as follows.

1.2.2.1 Does the Rare Subset of Highly Tumorigenic Cancer Cells Really Exist in a Solid Tumor?

As mentioned above, the high tumorigenicity is an essential characteristics for the cancer stem or stem-like cells isolated from human cancer tissues. In nearly all these reports, the tumorigenecity is determined by nude mice engraftment of a cell surface marker-based subpopulation of human cancer cells. However, Andreas Strasser’s group from Australia reported that tumor cells from some genetically engineered leukemia cells can give rise to tumors in syngeneic mice [65]. The tumorigenecity was shown by inoculation with a small number of these tumor cells, independent of the presence or absence of surface markers. This report implies that the cancer stem cell hypothesis requires further evidence of a tumorigenecity test with stem or stem-like cells isolated from tumors either induced by chemical carcinogens or spontaneous tumors from transgenic mice in syngeneic mice.

The other important challenge is from Sean Morrison’s laboratory in Michigan based on experiments on human melanoma in NOD/SCID mice with an additional defect of interleukin 2 receptor γ chain (IL2Rγ) [66]. They found that human melanoma cells were tumorigenic even by unselected single cell injection in matrigel. According to their calculation, human melanoma cells are tumorigenic at a dose of 1 out of 4 cells, implying that tumorigenic cells are not the rare subpopulation as suggested by cancer stem cell hypothesis. However, the normal human hemopoietic cells are also successfully engrafted in their mice model [67]. Thus, this animal model allows normal stem cells to grow, thereby reducing the threshold in their mice model to distinguish the growth of malignant from non-malignant cells.

As a whole, beside these two reports from leukemia and melanoma, results documented in most prevalent cancers provided strong evidence supporting the existence of a highly tumorigenic cell subpopulation in cancer. Moreover, we have to emphasize that the significance of results from xenograft experiments in NOD/SCID mice to test the “tumorigenicity” cannot yet be ignored. The high “tumorigenicity” revealed by some marker-selected cancer cells did demonstrate
that these cells can cross the species barrier from human to mouse and break through the immune defense system, such as the residual macrophages and natural killer cells [68]. Presumably, we can use the malignant potential as the term to replace the tumorigenicity, because this surface marker-based sorting can select cells with high malignant potency in xenograft tumor formation.

1.2.2.2 Diversity of Surfaced Markers in Cancer Stem-Like Cells Isolated from the Same Type Cancer

The diversity in immunophenotypic identities of cancer-initiated or cancer stem-like cells is isolated from the same type of cancer. It is still a puzzle that cancer stem-like cells reported in cancer patients from the same tissue origin have different immunophenotypic markers. For example, in HCC, at least four markers, CD133⁺, EpCAM, OV60 and CD90 have been identified [69-72]. The heterogeneity of cancer stem cell (CSC) based on immunophenotypes is also documented in nearly all types of cancer. One of the most plausible interpretations of the heterogeneity of marker-based characterization is the existence of cancer stem-like cells with different immunophenotypic characteristics in different HCC patients. Thus, HCC patients with different marker-based CSC may presumably represent different HCC subtypes. It remains to be clarified whether these subtypes of cancer from different patients may be caused by different genetic events occurring in different patients, resulting in different immunophenotypes of CSC. The other important issues about the heterogeneity of markers for HCC CSC are whether all of these markers do represent the hierarchical organization. If these markers are residing in the hierarchical lineage, it will reconcile well with the stem cell hypothesis. If not, we could assume that some of the HCC patients may have their highly malignant cells derived from non-progenitor cells due to gene mutation, deletion or amplification according to the “clonal evolution hypothesis” [73, 74]. In this respect, we can find these highly tumorigenic cells without any markers relevant to those in the hierarchical organization, nor with common markers in different patients. In fact, the cancer stem cell hypothesis and clonal evolution model may not be completely mutually exclusive because of the possible retrograde differentiation of cancer cells after initiation. All these complex features of CSC hypothesis will be extensively described and discussed in the succeeding Chapter 7.

1.3 Cancer is a Systems Disease—A Disease of Systems Dysregulation, Characterized by Abnormal Growth of the Defined Tissue or Organ

It has been a century-old concept that Virchow, the founder of cell pathology, defined cancer as a disease of abnormal, autonomous growth of cells from a
defined tissue or organ. Since then, the rapid progress in cell biology, biochemistry, genetics, cytogenetics, molecular biology, genomics, epigenomics, proteomics and metabolomics, has promoted great achievements in understanding the cell and molecular mechanism of cancer cells, cancer development and its progression.

In recent years, a vast number of reports were documented about the genetic, epigenomic and molecular alterations and the accompanying changes in signal pathways, apoptosis, DNA replication, cell cycles, etc., and relevant changes in cell behavior, including cell proliferation, invasion and metastasis. Among these changes, the deletion and mutation of tumor suppressor genes, such as p53, Rb, PTEN, etc., as well as mutation, gene amplification of oncogenes such as Ras and others, can be used to interpret the major intrinsic cellular alterations to initiate carcinogenesis and cancer progression.

The genomic and epigenomic alterations and the relevant changes in signal transduction will be extensively described in Chapter 3.

1.3.1 Systemic Regulatory Systems to Control the Host-Cell Homeostasis

Although great progress has been achieved in the understanding of molecular mechanism of cancer, many aspects of carcinogenesis and cancer development remain unclear. Particularly, we do not understand what are the host responses to the exposure of chemical and biological carcinogens, what are roles of mental stress in carcinogenesis and what are the defects in human host during the course of cancer development of its progression. All these puzzles make us to consider that cancer development may be a much more complex mechanism than what we had thought. Based on the reasons we address in following sections, we define the cancer is a systems disease characterized by abnormal growth of a defined tissue or organ, and we propose the hypothesis of deregulation and dysregulation of the two levels of host regulatory systems.

1.3.1.1 Cancer is a Disease with High Mortality, yet not with High Incidence among All Human Diseases

Though cancer accounts for one of the highest ranked diseases in terms of mortality, the overall incidence of cancer is about at least one magnitude less than cardiovascular diseases and diabetes. According to WHO data, the overall incidence of cancer is only 181.6 out of one hundred thousand in the global population (WHO, World Cancer Report 2008). However, chemical carcinogens are highly accessible from food, air and other sources in the environment. In the context of HBV infection, only a very small proportion of HBV carriers turn out to develop HCC. Furthermore, from the concept of genetic alteration, mutation is a quite common event which occurs at a frequency of about $>10^{-9}$ among all
dividing cells. Concerning the vast amount of cell divisions occurring in the human body all the time, we can presume that cells with a mutation threat to human health might not be a rare event, discarding those mutations with no hazardous effect on cell proliferation or survival. Therefore, a paradox exists between the high incidence of cell genetic changes and the relatively low potential of cancer formation. The only reasonable interpretation of this discrepancy is the presence of an extremely powerful defensive mechanism in the human body to counteract the chemical or biological carcinogenic factors as well as to eliminate the hazardous mutated cells.

1.3.1.2 Hypothesis of Two Level Systemic Regulatory Systems to Maintain the Host-Cell Homeostasis

We presume that there are “two-level” systemic regulatory systems in the human body: one is the “central” system to control the organs and tissues; the other is the “local” system to regulate all the cell components at an organ or tissue level.

1. The central systemic regulatory system

The central control system comprises the regulatory pathways from the cerebral cortex-hypothalamus-pituitary-adrenal axis and autonomic nervous systems to govern endocrine and immune organs. The neuro-endocrine-immune loop constructs a complex network in regulation of biological, metabolic and immune activity to maintain the global homeostasis.

2. The existence of a “local” regulatory system at an organ/tissue level

Up to now, it seems we almost completely ignore the regulatory mechanism in a parenchymatous organ, such as the liver. We will hypothesize here about what the existence of a non-neuronal/neuronal neurotransmitters-endocrine-immune regulatory system presents in the liver. The evidence to support this hypothesis will be discussed in detail in Chapter 2. Here, we only emphasize the major considerations in the present context:

(i) First of all, the liver is not only a metabolic organ, but also an immune organ. The coherent hepatic immune cell system and its function are described in Chapter 8.

(ii) Secondly, our laboratory has for the first time demonstrated the hepatocytes can synthesize and secrete acetylcholine, constructing a non-neuronal cholinergic autocrine/paracrine system. Furthermore, we found that hepatic stellate cells can synthesize acetylcholine, noradrenaline, adrenaline and dopamine (Zhigang Zhang, et al., to be published). All the relevant neurotransmitter receptors are expressed in hepatocytes, and part of them in stellate cells and immune cells. Therefore, in addition to neurotransmitters derived from autonomic nerve endings mostly at sinusoids, the liver itself can produce neurotransmitters and from an autocrine/paracrine loop. These findings strongly imply that the liver is also a neuro-transmitter-generating organ.

(iii) Thirdly, the normal and non-cancerous liver can express hormone receptors, such as androgen and estrogen receptors, which can be potentially
modulated by neurotransmitters. Furthermore, estrogen and androgen receptors are expressed in HCC and noncancerous liver tissues in both male and female HCC patients. It is implied that sex hormone receptors may play some important yet not defined biological function in the human liver.

(iv) Based on the above evidence, we postulate that the liver itself has neural transmitters, (both the neuronal and non-neuronal)-endocrine-immune regulatory systems, to govern the hepatic biological, metabolic and immune functions. The dysregulated function of this system may play an important role in HCC development and its progression.

(v) Though we have the above evidence to support the postulation of the presence of a local regulatory system in the liver, the evidence that such a system may also exist in other organs or tissues remains to be further explored. However, non-neuronal neurotransmitters have been found in other organs, such as lung, pancreas and gastro-intestinal tract. The neuro-endocrine-immune regulatory system in these organs or other tissues is waiting to be validated by extensive investigation.

(vi) In HCC patients, the non-cancerous liver functions as the local regulatory system under the control of the central system. After HCC developed, the liver in which the tumor resides represents the organ with progressive dysregulation both at the central, and maybe more importantly, at the local level. The normal neuro-endocrine-immune network is further deteriorated in favor of cancer growth, invasion and metastasis.

3. Requirement to clarify the nomenclature of the cancer microenvironment

As we described in the previous section, the cancer or tumor microenvironment is defined as the milieu contributed to by all the cell components and the extracellular matrix. However, in the case of HCC patients, the non-cancerous liver has been misused as the HCC microenvironment. In fact, the cell components and even the matrix in HCC tissues are different from those present in the liver where the cancer resides. For instance, cancer cells, cancer-activated fibroblasts, neovasculature cells and the aberrant immune cell population in HCC are obviously different as compared with hepatocytes, biliary tubules, stellate cells, fibroblast, sinusoidal and vasculature endothelial cells, küpffer cells and other immune cells. Therefore, we have to seriously confine the cancer microenvironment to the milieu inside the cancer. On the contrary, the non-cancerous liver is a part of the host, which reflects the dysregulated regulatory system at the organ level and probably also the deregulated central regulatory system. Obviously, intimate cross-talk and interaction are expected to be conducted between the cancer microenvironment and the local/central regulatory system. This interaction is an intriguing subject to be further explored for elucidation of cancer and host interaction in HCC progression.

Based on the concept of systemic regulation, the strategy for cancer treatment should be re-evaluated. As cancer is a systems disease, cancer patients should be treated as a whole, instead of targeting only the cancer itself. Thus, a new therapeutic strategy should be considered. In addition to the current use of treatment targeting the cancer, such as surgical resection, radiation and
chemotherapy, the reconstitution or re-establishment of the normal systemic regulatory systems, including the restoration of neural, endocrinal and immunological disorders, and the relevant deteriorated network of signal transduction, should be a new perspective for cancer treatment.

1.3.1.3 Concept and Strategy of 4-Dimension Systemic Integrated Biology of Diseases

How to investigate the multiple-level systemic regulation, we addressed here the concept and strategy of 4 dimensional systemic integrated biology for cancer as shown in Fig. 1.1. The dimension 1 (horizontal axis) is the integrated Omics studies, from genomics, epigenomics, transcriptomics, proteomics, metabonomics, eventually to construct the dynamic information networks. The dimension 2 (vertical axis) indicates, in general, the integrated information of two-level host-cell systemic regulation. The top level is the central regulatory system, including the central nervous system, autonomic nervous system, hypothalamus-pituitary axis, endocrine and immune organs. The second level is the regulatory system at organ and tissue level, including the neuronal/non-neuronal neurotransmitters, endocrines and their receptors, immune system at tissue level interplayed by multiple types of cells, namely parenchymal/epithelial cells, stromal cells, vascular cells and immune cells. In case of cancer development and progression, there exists an additional regulatory system in cancer microenvironment, attributed to cancer/stromal/vascular/immune cells as previously described in Sections 1.1 and 1.3.1.2. These multiple-layer machineries of control construct a complex regulatory system in human cancer patients. The dimension 3 is the blood, as a window which can reflect the molecular changes from various organs or tissues, including the cancer and its microenvironment, in addition to blood circulation immune cells or other detached cells, such as circulating tumor cells (CTC). The dimension 4, not shown directly in the Fig. 1.1, is the time course which determines the progressive and dynamic changes during progression of diseases.

For studies of human individuals and cancer patients, only the cancer or noncancerous tissues and blood are accessible. However, we can use animal models to test the overall changes of host-cell multiple level-integrated biology as well as the systemic regulation. Once the essential molecules and their network have been found in the animal model, it would provide us the molecules to test and validate their functional roles in human patients. Moreover, the concept and strategy of systemic integrated biology might put some insight not only to cancer biology, but also to the research of the molecular mechanism for other chronic diseases, including diabetes, cardiovascular and autoimmune diseases.
1.4 Prospects and Implications

Based on the concepts and challenges in cancer biology we presented above, we can predict that the strategies for current and conventional research on cancer, particularly in HCC, might be cautiously under consideration. As we have emphasized, cancer is a well-organized tissue, and cancer cells consist of a subpopulation of the most aggressive cells or cancer stem-like cells. The biological behavior of all these cell components might be under the control of a “central” and “local” systemic regulatory network. In particular, considering the hypothesis that cancer is a disease resulting from systemic dysregulation, the therapeutic strategy for reconstitution or re-establishment of the homeostatic state of the neuro-endocrine-immune regulation and relevant signal pathways of the whole patient, both at “central” and “local” levels, may be potentially crucial. This is a new approach in addition to current surgical, radiation and chemotherapeutic treatment, so as to improve the survival rate of cancer patients.
References


References


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