Austin Journal of Nanomedicine & Nanotechnology

Open Access

Austin Publishing Group

Short Communication

Cancer Stem Cells, Tumor Microenvironment and Nanomedicine

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Received: June 14, 2018; **Accepted:** June 27, 2018; **Published:** July 04, 2018

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Problem: Chemotherapy is one of the current mainstream anticancer therapies using chemicals to induce apoptosis by damaging DNA and/or inhibiting mitotic division to kill rapidly dividing cancer cells [1]. Conventional chemotherapeutic strategy may exhibit initial success, but the eventual relapse of tumor growth is due to a greater resistance which recognized as the primary cause of chemotherapeutic failure for most human cancers [2]. Because of genetic instability in cancer cells, nonrecurring mutations and large genomic alterations generate vast heterogeneity, giving rise to tumors which comprised subpopulations of distinct cells. Some of the tumor cells have been known as intrinsic resistance to the "achievable" doses of anticancer drugs, while other tumor cells are initially sensitive but become resistant during the course of treatment. There are three important chemo-resistant issues: 1) the pharmacological factor, which is the "inadequate" drug concentration at the tumor site, causes chemo-resistance; 2) cellular factor, which is a certain type of cancer cells, such as progenitor Cells/Cancer Stem Cells (CSCs), renders a capability for the subset of cancer cells evading slaughter of a variety of structurally and functionally chemo-agents [3]; 3) tumor microenvironment factor, which is dictated in one way or another, by a specific composition for tumor initiation and induction of tumoral angiogenesis, and for invasion and metastatic processes [4].

CSC and its niches: CSCs, a sub population of tumor cells with the capabilities of self-renewal and differentiation potentials, contribute to tumor initiation, progression, and recurrence. CSC has been accepted as the most significant factor for the therapeutic failure. Although the mechanism is poorly understood, the CSCs, in fact, are protected physically by multiple lines of defense to resist chemotherapy. To resemble normal stem cells which generally located at places that are less exposed to potential external attacks, CSCs also take the maximal advantage of the CSC niches they are localized in. CSCs can differentiate into tumor cells under some circumstances, while the non-CSC-tumor cells may dedifferentiate into CSCs. Evidence suggests that CSCs and non-CSCs are not in amotion less but in a dynamic equilibrium state. The chemo-agents can kill the non-CSCs but may not the CSCs, especially those CSCs hidden in the CSCs niches. The niche concept is generally accepted and CSC niches are thought to be the important places to maintain a balance between self-renewal and differentiation. CSC niches are particular compartments consist of extracellular matrix and other stromal cells including endothelial cells, macrophages, immune cells, fibroblasts and stem cells. Therefore, the therapy resistance of CSCs niches could be through either extracellular matrix protein-cell or cell-cell communication. There is a vast need for new approaches to improve current therapeutic strategies that will not only increase the chemo-agents concentration at the CSC niches but also target to CSCs and thereby to kill them.

Tumor microenvironment: Different from CSCs niches, tumor microenvironment is a more broad term. The tumor microenvironment includes, 1) the tumor stroma composed of fibroblasts, endothelial cells, immune cells, and the ECM; 2) the epidermal microenvironment where the tumor is originated from; 3) different sub compartments within the tumor itself; and 4) different effectors of inflammatory system, soluble molecules of hypoxia factors, nutrients and metabolic products. Interactions between tumor cell and its microenvironment contribute to the malignant behavior of tumor cells, including initiation, progression, metastasis, angiogenesis, migration, and invasion. Generally, the tumor microenvironment contains many drug resistant factors, including stromal cells, soluble molecules such as interleukins, and ECM components such as fibronectin and collagen, all that may contribute to decreasing the chemo-drug activity and result in residual tumor cells, especially the CSCs. Both genetic and epigenetic changes accompanied by crosstalk with the tumor microenvironment make cancer therapy remaining a big challenge. Unlike acquired resistance which is a consequence of adaptive genetic and epigenetic mutation due to chemotherapy, most microenvironment-mediated resistance is inherent in tumors. However, CSCs and tumors may also affect their niches or microenvironment.

Nanomedicine: Given that the existence of CSCs is a primary obstacle to cancer therapy, a tremendous amount of effort has been put into the development of anti-CSC strategies, and several potential approaches to kill therapeutically-resistant CSCs have been explored targeting CSCs surface markers and destroying the tumor microenvironment. An increasing number of therapeutic agents (e.g. small molecule drugs, nucleic acids and antibodies) to selectively target CSCs have been proposed, but most of these agents are limited for clinical application. Nanotechnology based drug delivery approaches hold great potential for tackling the limitations impeding clinical applications of those CSC-specific agents, such as poor water solubility, short circulation time and inconsistent stability [5]. Nanotechnology is at the forefront of both targeted drug delivery and intrinsic therapies. Nanoparticles based encapsulation of chemo-drugs allows much more localized delivery increasing the quantity of drugs absorbed by tumor cells both but reducing significantly the side effects on healthy tissues in the body. Using nanotechnology can overcome the chemo-resistance, and this is exemplified by the followings [3,6-8]: 1) modification of physical properties can improve the nanopartilces travel to cross "biological barrier" thereby increase

Citation: Li Y. Cancer Stem Cells, Tumor Microenvironment and Nanomedicine. Austin J Nanomed Nanotechnol. 2018; 6(1): 1046.

the local concentration of drugs, i.e., chitosan is generally used for such modification; 2) Near-Infrared (NIR) at certain wavelength can trigger nanopartilces to generate heat. For example, the NIR-triggered gold nanoparticles have drawn much interest for purposes either directly tumor cells thermo ablation or drug-delivery with controlled drug release; 3) the size and shape of a nanovector such as nanoshell and nanorod scan enhance by orders of magnitude the amount of drug delivered to the tumor site; 4) engineering nanoparticles can create targeting nanovectors to bind for appropriate malignant tissues and cancer cells. One of the popular options for biological targeting is using antibodies on the surface of nanovectors, resulting in a combined effect of enhanced delivery and intrinsic therapy.

In addition, nanotechnology has been also applied to cancer for diagnosis and treatments [9,10]. Some molecules/proteins produced by tumor cells spreading in the tissue/blood are commonly used in cancer detection. However those molecules/proteins are present mostly in very low concentrations to be efficiently detected in early phases of diseases. The development of nanovectors, such as nanoparticles, can be loaded with some imaging agents and such technologies can lead to more sensitive detection of the biomarkers for earlier diagnosis [11]. Early detections of cancers are critical because it allows early and less burdensome treatments, increasing the chances of recovery. Nanoparticles are also applied for accurate cancer imaging. For example, iron oxide nanoparticles are one useful tool for cancer imaging. When the iron oxide nanoparticles engineered with a specific coating which is with high affinity to bind particularly well to the tumor cells. The magnetic properties of iron make the nanoparticles as a perfect imaging agent for MRI-scans [12]. The size and concentration of the nanoparticles in the tumor allow a very high resolution and an accurate mapping of the cancerous lesions. Rely on the imaging details, surgeons can thus to select a properly surgical plan to remove the tumor.

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