EDITORIAL

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The Legacy of Mesenchymal Stem Cells in Vindicating the Clonal Evolution Model of Cancer

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Introduction

Organogenesis and tumorigenesis seem to be following a set pretty similar instructions and pathways and tumors, like any other organ, can be seen as the summation of many different cell types. However, unlike normal tissues, intercellular networks in cancer show high degrees of robustness and plasticity, employing other cellular networks in favor of their own growth1. The integrated hallmarks of cancer were first described by Hanahan and Weinberg in 20002, and was updated in 2011 by the same scientists3. They have described 10 hallmarks including: 1) self-sufficiency in growth signals, 2) not responding to antigrowth signals, 3) unlimited proliferation, 4) resisting apoptosis, 5) genomic instability, 6) angiogenesis, 7) deregulated metabolism, 8) inflammation, 9) escaping immune destruction, and 10) tissue invasion and metastasis3, all of which have stood the test of time as being integral components of most forms of neoplasms. These unifying hallmarks are a reflection of the network structure of human cells dictating which genetic/epigenetic alterations are viable and in favor of tumor formation and progression. Among all the theories trying to explain the origins and hallmarks of cancer since Hippocrates4, clonal evolution and the stem cell hypothesis are the two theories that explain hallmarks of cancer the best5. For the purpose of this editorial our focus will be on the clonal evolution theory.

The clonal evolution model of cancer is based on the premise of natural selection operating in any system with components of varying reproductive/survival potential6. Cancer clone evolution takes place within a mature tissue ecosystem which has evolved over billions of years and hallmark properties of cancer are the results of disruptions in molecular and cellular networks established during the emergence of multicellularity1. Like any other multicellular organ, interactions between cancer cells and their tissue habitats are reciprocal and frequently cancer cells remodel normal tissue micro-environments to their own competitive advantage, which will then be called tumor micro-environment (TME).

Within TME, will be formed a set of organized networks to guarantee tumor cells' survival and proliferation. Wang and colleagues7 have categorized these networks in seven groups, including: the survival network, mutating network, differentiation network, angiogenesis-inducing network, immune-escaping network, epithelial-mesenchymal transition (EMT) network, genome duplication network, metabolic network, and stroma network7. These cellular and molecular networks and hallmarks of cancer can be described as resultants of cross-talks among three major cell types in TME: neoplastic cells, immune cells, and mesenchymal (stromal) stem cells (MSCs) (Figure 1).

MSCs are major components of TME and although controversial, they are mostly known for their tumor promoting effects8. They play critical roles in re-programming of TME in favor of tumor progression, by several mechanisms, including induction of sustained proliferative signals, inhibiting apoptosis, transition to tumor associated fibroblasts (TAFs), promotion of angiogenesis, stimulation of EMT, suppression of immune responses, and consequential promotion of tumor 9. Furthermore, from another perspective, we have previously proposed that in favorable conditions MSCs are capable of giving rise to sarcomas, carcino-sarcomas, and

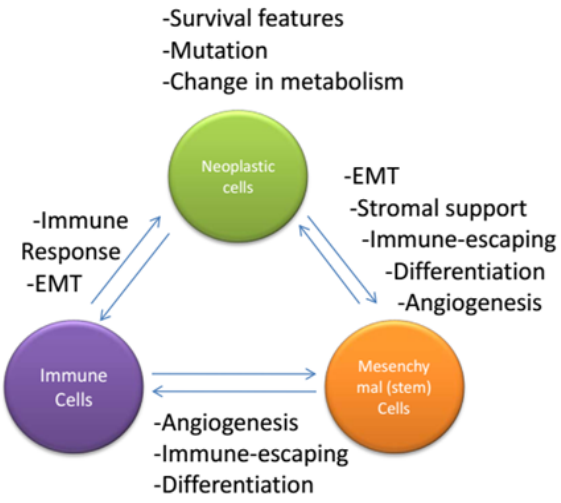

Figure 1. Organized Networks within Tumor Microenvironment to Guarantee Tumor Cells' Survival and Proliferation

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carcinomas10. These are not surprising, since MSCs are well known for their tissue rescue effects in injuries and inflammations, trying to do the same in TME.

Although bone marrow is considered the main source of MSCs (BM-MSC), resident tissue MSCs, for example adipose-derived-MSCs (ACSs), show the same tissue salutary effects and tumor promoting properties to a large extent11. However, MSCs derived from different tissues show different cellular and molecular properties12, even being in different stages of stemness. These diversities will affect the cross-talk among these cells, neoplastic cells and immune cells, causing tumor heterogeneity, different tumor behaviors, and different response to host defenses and clinical therapies.

Considering the diverse behaviors of MSCs, it is logical to assume that MSCs isolated from different types of cancer, the same kind of neoplasms in different individuals, and even the same neoplasm of the same person in different stages, would show different cellular and molecular properties. As mentioned previously, the interactions in TME are reciprocal, and the nature of the cancer and host immune responses cannot be ignored in designation of MSCs' properties. Comparing the characteristics of MSCs isolated from different tumors, the same tumor in different stages, resident MSCs of a premalignant lesion with those of malignant ones would be helpful in understanding of these cells' behavior through progression of cancer, anticipating neoplasms' behavior in accordance to observed MSCs' properties, designing personalized therapies, and defining the proper characteristics of MSCs which can be used safely as options for cell therapies.

Conflict of interests

None to be declared.

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References

Gerdes MJ, Sood A, Sevinsky C, et al (2014). Emerging understanding of multiscale tumor heterogeneity. *Front Oncol*, **4**, 366.

Ghaderi A, Abtahi S (2018). Mesenchymal stem cells: Miraculous healers or dormant killers?. *Stem Cell Rev*, **14**, 722-33.

Greaves M, Maley CC (2012). Clonal evolution in cancer. *Nature*, **481**, 306-13.

Hanahan D, Weinberg RA (2011). Hallmarks of cancer: the next generation. *Cell*, **144**, 646-74.

Hanahan D, Weinberg RA (2000). The hallmarks of cancer. *Cell*, **100**, 57-70.

Paduch R (2015). Theories of cancer origin. European journal of cancer prevention. *Eur J Cancer Prev*, **24**, 57-67.

Papaccio F, Paino F, Regad T, et al (2017). Concise review: Cancer cells, cancer stem cells, and mesenchymal stem cells: influence in cancer development. *Stem Cells Transl Med*, **6**, 2115-25.

Razmkhah M, Abtahi S, Ghaderi A (2018). Mesenchymal stem cells, immune cells and tumor cells cross talk: A sinister triangle in the tumor microenvironment. *Curr Stem Cell Res Ther*, doi: 10.2174/1574888X13666180816114809. [Epub ahead of print].

Sabol RA, Bowles AC, Cote A, et al (2018). Therapeutic potential of adipose stem cells. *Adv Exp Med Biol*, doi: 10.1007/5584_2018_248. [Epub ahead of print].

Trigos AS, Pearson RB, Papenfuss AT, Goode DL (2018). How the evolution of multicellularity set the stage for cancer. *Br J Cancer*, **118**, 145-52.

Wang E, Zaman N, McGee S, et al (2015). Predictive genomics: a cancer hallmark network framework for predicting tumor clinical phenotypes using genome sequencing data. *Semin Cancer Biol*, **30**, 4-12.

Wu M, Zhang R, Zou Q, et al (2018). Comparison of the biological characteristics of mesenchymal stem cells derived from the human placenta and umbilical cord. *Sci Rep*, **8**, 5014.