Depolarization or hyperpolarization: Emerging role of altered bioelectricity in breast cancer metastasis

Hangang Yu

Department of Physiology and Pharmacology, School of Medicine, Health Sciences Center, West Virginia University, Morgantown, WV 26506, USA

Cell membrane potential (Em) is essential for electrical activities in excitable cells such as neurons and heart cells. Accumulating data has now revealed an important role of Em in non-excitable cells such as epithelial cells. Alterations in Em (depolarization – Em becoming more positive, or hyperpolarization – Em becoming more negative) play a crucial role in controlling cell cycles.1

In breast cancer biopsy independent of estrogen receptor (ER) or progesterone receptor (PR) presence, Em was found to be -63 mV, significantly depolarized as compared to Em (about -60 mV) in normal breast cells.2 Depolarization has been proposed as a biomarker for breast cancer.3

Membrane depolarization activates ion channels that are linked to hallmarks of cancer,4 such as initiation, invasion, and metastasis. Voltage-gated sodium channels (VGSCs) have been demonstrated to contribute to breast cancer metastasis.5 Depolarization-triggered electrical excitability has now been observed in metastatic breast cancer cells.6

In a recent issue of EBioMedicine, Payne et al. presented strong evidence for a novel hyperpolarization-driven metastasis in breast cancer cells in vitro and in vivo.7 The authors demonstrated that in triple-negative breast cancer (TNBC) patients, K⁺ channels are overexpressed, while Na⁺ and Cl⁻ channels are not, as compared to PR⁻/ER⁻ and HER2⁺ patients; overexpressing Kv1.5 or Kir2.1 in metastasis cell lines, MDA-MB-231 and MDA-MB-468, resulted in a significant membrane hyperpolarization associated with an enhanced invasion in vitro and metastasis in vivo; hyperpolarization caused changes in cell morphology, focal adhesion signaling required for cell migration and invasion, and increased the expression of genes associated with cell adhesion and MAPK signaling. They identified cadherin-11 as the key protein that drives migration induced by hyperpolarization; the authors proposed the use of FDA-approved K⁺ channel blockers to inhibit TNBC metastasis. They illustrated this idea by showing that an antiarrhythmic drug, amiodarone, can depolarize TNBC cell resting membrane potential and decrease metastasis to the lung in an MDA-MD-231 xenograft model.

While the findings are intriguing, an important question is raised. It has been well established that membrane depolarization is a biomarker for tumorigenicity - breast cancer cells have depolarized resting membrane potentials compared to normal breast cells. Numerous K⁺ channels have been reported to be overexpressed in breast cancer cells compared with normal breast cells. If hyperpolarization induced by overexpressing K⁺ channels can promote metastasis, why is overexpression of K⁺ channels associated with depolarized resting membrane potential in breast cancer cells? Another unanswered question raised by the Payne’s article is the use of amiodarone. Although it is an FDA-approved antiarrhythmic drug that can inhibit K⁺ channels, it is known that it can also block Na⁺ channel activity. Therefore, the amiodarone-mediated reduction of migration of TNBC cells could be explained by blocking Na⁺ channel activity, and the role of Na⁺ channels in metastasis has been well established.8,9

While genetic heterogeneity of breast cancer has been established,8 the data presented by Payne et al., may have suggested a possible heterogeneity in bioelectricity in metastatic breast cancer cells. It may be possible that not all breast cancer cells have depolarized Em. Investigation on resting membrane potential has been performed using traditional electrophysiological techniques, such as intracellular microelectrode and patch clamp on isolated single cells.8,9 While accurate, these techniques are low throughput and inefficient in studying heterogeneity of membrane potential in metastatic breast cancer cells. High-throughput techniques using membrane potential sensitive dye combined with advanced imaging technology may be able to detect Em heterogeneity in breast cancer cells.

Heterogeneous bioelectricity in cancer cells may be caused by differential expression of ion channels. Accumulating data has been revealing an exciting fact: the voltage-gated ion channels play an important role not only in the excitable cells, but also in traditionally defined non-excitable cells such as epithelial cells. The epithelial to mesenchymal transition (EMT) is an initial step in cancer metastasis. Revealing the mechanistic insights of altered membrane potential (whether depolarization or hyperpolarization, and probably a mixture

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E-mail address: hyu@hsc.wvu.edu
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of depolarized and hyperpolarized cells) and ion channel activities during EMT in breast cancer cells should provide new ideas for repurposing drugs (whether K\(^+\) channel blockers and activators, or Na\(^+\) channel blockers) for effective treatment of metastasis and therapeutic resistance in triple-negative breast cancer with fewer side effects.

Contributors
Hangang Yu wrote this commentary.

Declaration of interests
None.

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