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COMMENTARY

Invited Commentary on: Can CD44+/CD24- Tumor Stem Cells Be Used to Determine the Extent of Breast Cancer Invasion Following Neoadjuvant Chemotherapy?

Jeong Eon Lee, Seok Jin Nam

Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

The article published by Wu et al. [1] in *Journal of Breast Cancer* proposed that the presence of so called 'tumor stem cells' may be an additional parameter to determine the extent of breast cancer invasion in the setting of surgery following neoadjuvant chemotherapy. However, this article has some noteworthy concerns. The first one is regarding the concept of 'tumor stem cells'. The second is about the markers the author used in the article. The third is their way of determining the tumor margin.

It seems that the authors are arguing CD44(+)CD24(-) cells as human breast 'tumor stem cells.' However, their argument is not so well accepted since the tumor stem cell is not a synonym of a tumor-initiating cell. While several studies provided indirect evidence for the existence of mammary stem cells in human and in mice, these stem cells have not yet been prospectively isolated at a single cell level in human breast cancer. According to the cancer stem cell model, the tumorigenic stem cells are maintained through self-renewal and have the ability to differentiate into non-tumorigenic cancer cells [2]. It has been postulated that the cancer stem cells are from the normal stem/progenitor cells as a result of accumulated mutation during the self renewal process. However, a recent study suggests that this counterpart-relationship of the human breast epithelial hierarchy is not necessary to develop a breast cancer; an aberrant luminal progenitor population is a target for transformation in BRCA1-associated basal tumors [3]. Because a single tumor stem cell that can repopulate the heterogeneity of human breast cancer has not been identified yet, it has not been clear whether there is a certain specific 'tumor stem cell' or 'tumor initiating cells' which have tumorigenic capability.

Correspondence: **Seok Jin Nam**
Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Ilwon-dong, Gangnam-gu, Seoul 135-710, Korea
Tel: +82-2-3410-3478, Fax: +82-2-3410-6982
E-mail: seokjin.nam@samsung.com

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While the monumental report proposed that the CD44(+)CD24(-/low) might be the characteristics of tumorigenic breast cancer cells, there still has been little consensus on the suitable markers for the breast cancer stem cells [4]. It is still not clear whether CD44(+)CD24(-) itself is true and definite characteristics of human breast tumor stem cells or not. For example, aldehyde dehydrogenase (ALDH) was suggested as a useful marker for enriching tumor-initiating cells in immunodeficient mice [5,6]. CD44(+)CD24(-/low) subtype can be subdivided by ALDH1 biomarker, and interestingly, the overlap between CD44(+)CD24(-/low) and ALDH1 phenotypes in breast cancer seems to be very small [5,7]. Regarding the intrinsic molecular subtypes, basal-like tumors contain a higher percentage of cells with CD44(+)CD24(-/low) and ALDH1-positive cells [7]. CD44(+)CD24(-/low) might be considered as the markers for basal subtypes rather than those of breast tumor-initiating cells, and CD44(+)CD24(-/low) alone cannot be considered as a definitive marker for stem cell characteristics.

In this article, the authors also suggest that six categories can be classified from the pattern of cancer cells and stem cells, which are identified in the immunofluorescence studies performed on tissue sections obtained from surgical resection of tumors following neoadjuvant chemotherapy. According to the presented methods, $0.5 \times 0.5 \times 0.5$ cm^3 sized sections were obtained at 1 cm intervals from the tumor diameter up to 3 cm outside the maximum diameter of the tumor. We are seriously concerned whether it is a sound way to identify the border of breast cancer and remove a piece of tissue at 1 cm intervals in removed fresh breast specimen after neoadjuvant chemotherapy with the naked eye. After neoadjuvant chemotherapy, the identification of patients with a pathologic complete response before surgery often becomes difficult by physical examination. Moreover, imaging studies such as mammography, ultrasonography or magnetic resonance imaging cannot reliably assess degree of response. Neoadjuvant chemotherapy-induced tumor regression is usually patchy, remaining islands of viable

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tumor cells, and it is not concentric [8]. In case of the remained tumor nests after neoadjuvant chemotherapy, it can be hardly feasible to identify tumor margins with the naked eye. We are deeply apprehensive that this method may not be always possible and repeatedly performed in a standardized way.

A breast cancer resistant to the chemotherapy or radiation may contain higher levels of CD44(+)CD24(-/low) cells [9]. However, this does not necessarily mean that 'tumor stem cells' are resistant to the chemotherapy or radiation because of the recent evidences that CD44(+)CD24(-/low) is not an absolute marker of breast cancer stem cells. This study is very interesting in trying to find a pattern between the distribution of CD44(+) CD24(-/low) cells from the tumor margin. However, in our humble opinion, careful consideration should be given from the above viewpoints.

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