Deep Learning-based Virtual Immunohistochemical HER2 staining of Label-Free Breast Tissue

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Abstract: We present deep learning-based virtual immunohistochemical (IHC) HER2 staining of label-free breast tissue sections, matching the standard IHC HER2 staining performed by histotechnologists. © 2022 The Author(s)

1. Introduction

The immunohistochemical (IHC) staining of tissue sections is widely practiced in life science research and the clinical evaluation of various diseases. By selectively identifying the specific IHC biomarkers, such as the human epidermal growth factor receptor 2 (HER2) that is associated with aggressive breast tumor development, the IHC staining of tissue provides a reliable and effective way to examine the disease development, direct the targeted therapies and predict the therapy response [1]. However, the conventional IHC staining is relatively complicated, costly, and time-consuming, which involves laborious sample treatment steps and toxic chemical compounds.

Here we present a label-free virtual IHC staining method that transforms the autofluorescence microscopic images of unlabeled breast tissue sections into their bright-field equivalent microscopic images using deep learning, matching the standard IHC HER2-stained images of the same tissue samples (Fig.1a) [2]. The quantitative analysis of the blind evaluation results by three board-certified breast pathologists revealed that the HER2 scores determined by inspecting the virtually stained IHC images are as accurate as their standard IHC stained counterparts. Furthermore, the virtually stained HER2 images demonstrated a comparable staining quality in various sub-cellular details with respect to their standard IHC stained counterparts [2].

2. Methods

The presented virtual HER2 staining method employs a generative adversarial network (GAN) to perform image-to-image transformations using autofluorescence microscopic images as input. The autofluorescence input images were captured using unlabeled tissue sections with 4 standard fluorescence filters (i.e., DAPI, FITC, TxRed, and Cy5), and were then precisely registered to the ground truth bright-field microscopic images of the same sections after standard IHC staining; this is only needed during the training phase, which is a one-time effort. The GAN consists of a generator network based on the attention-gated U-net structure [3] and a discriminator network based on the residual convolutional neural network structure. The network models were optimized by the AdamW optimizer using PyTorch (Meta). A total of 25 whole slide images (WSIs) from 19 unique patients were used in the training and evaluation of the network models.

3. Results and Discussion

Fig. 1b compares the virtual HER2 images inferred by the trained models against their corresponding ground truth, bright-field images captured from the same tissue sections after the standard IHC staining by histotechnologists. Three board-certified pathologists confirmed that the virtually stained images accurately revealed the HER2 biomarker distribution and showed a high degree of agreement compared to the standard IHC stained images, with no significant perceptible differences in intracellular features such as nuclear details and membrane clarity [2].

To quantitatively evaluate the efficacy of the presented virtual IHC staining method, we employed a cross-validation approach and trained separate network models to generate 12 virtual HER2 WSIs for blind evaluation. The three board-certified breast pathologists were asked to grade the HER2 scores (i.e., 3+, 2+, 1+, or 0) for each WSI without knowing if it was virtually stained or standard IHC stained. The statistical evaluation results revealed that more cases were correctly scored based on the virtual HER2 WSIs compared to the standard IHC HER2 WSIs, showing that our method enabled a competitive HER2 scoring accuracy compared to the standard HER2 evaluation based on chemically-prepared IHC slides. Furthermore, we had our pathologists blindly evaluate the staining quality of 120 image pairs cropped from the virtually stained and standard IHC WSIs. This quantitative analysis confirmed that the virtually stained images exhibit a comparable staining quality with respect to the standard IHC stained images in terms of nuclear detail, membrane clearness, and absence of staining artifacts [2].

Compared to standard IHC staining procedures that typically take ~1 day/slide, involving toxic chemicals and laborious steps performed by histotechnologists, our virtual HER2 staining method only takes ~12 sec for 1 mm^2 tissue using a consumer-grade computer without relying on any delicate chemical treatment steps. Our method also generates highly reproducible and consistent staining results, minimizing the commonly experienced staining variations and artifacts observed in standard IHC staining. This method can be potentially extended to other types of IHC biomarkers and be adapted to non-fixed, fresh tissue samples or frozen sections during surgical operations.

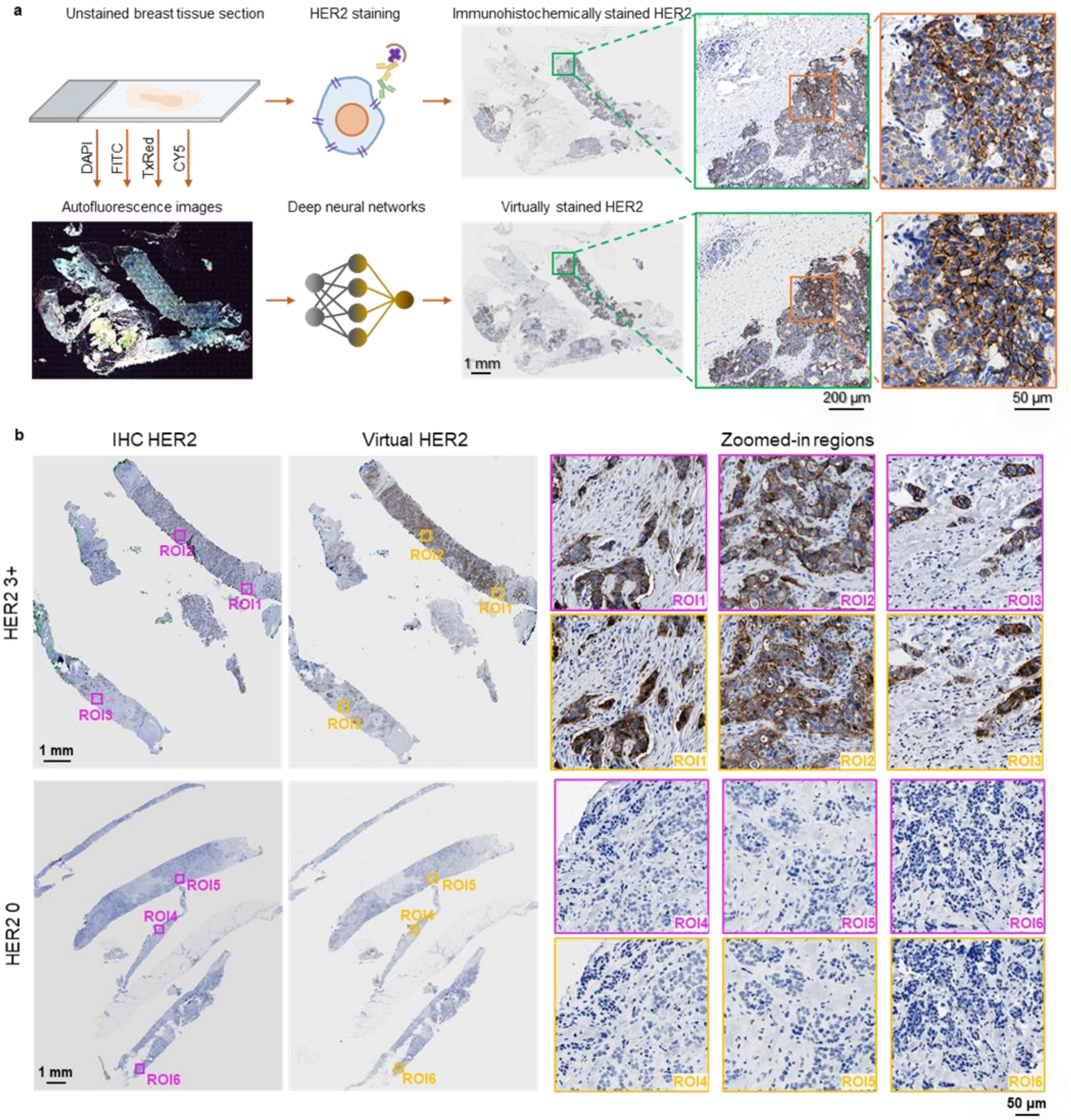

Fig. 1. Virtual IHC HER2 staining of label-free breast tissue via deep learning. (a) The virtual HER2 staining workflow using unlabeled tissue sections (bottom) bypasses the tedious and costly standard immunohistochemical HER2 staining (top). (b) Comparison of virtual and standard IHC HER2 staining of a HER2 positive (3+) and a HER2 negative (0) breast tissue section.

4. References

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