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Editorial

Clinical Pathology in The Future: do Genetic Analyses Replace The Morphological Observation?

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Rudolph Ludwig Carl Virchow, the father of modern pathology, said '*Omnis cellula e cellula*' (every cell arises from another cell) through his microscopic observation one and a half century ago. Cancer cells, naturally, arise from normal cells of the human body. Compiled light microscopic observation of cancer cells, ever since the era of Dr. Virchow, has contributed to the composition of the current histopathological classification of cancer subtypes, which is fundamentally based on the pure morphological features of cancer cells including the expected cells of origin (resemblance) and the degree of dedifferentiation (or estrangement) from the normal counterparts: e.g. adenocarcinoma originated from glandular cells and squamous cell carcinoma originated from squamous epithelium. With the histopathological classification and definition of each cancer subtype, which is globally standardized and published by the WHO, a number of clinical and preclinical researches have been carried out in systematically organized fashions, leading to the advance in diagnosis, treatments and prognosis prediction. Pathological evaluation of neoplastic lesions is, thus, essential in current clinical practice.

Driven by the technological improvements in molecular genetics including microarrays and next-generation sequencers, gigantic information of cancer genome and epigenome is now bringing about reform of clinical cancer diagnosis and histopathological classification. The most common histopathological subtype of breast cancer is the "invasive carcinoma of no special type" (up to 75% of invasive breast carcinoma cases), according to the current WHO classification (WHO Classification of Tumours of the Breast, IARC, 4th edition, Lyon 2012). Gene expression analyses by Perou., *et a*l. [1] and other groups proposed subclassification (called as the 'intrinsic subtypes') of the invasive breast carcinomas into 5 groups (13th and 14th St. Gallen international breast cancer conference in 2013 and 2015) [2,3]: i.e. hormone receptor-positive luminal A type (low proliferation), luminal B type (high proliferation), HER2-enriched type, (triple negative) basal-like type and (triple negative) unclassified type. The subclassification by intrinsic genetic alterations of cancer cells is now proven to be essential because it critically links to the clinical prognosis and response to anti-cancer drugs. Recently, three big papers about breast cancer genetics have further come out: i) Castro., *et al*. identified regulators of genetic risk of breast cancer [4], ii) Marcotte., *et al.* summarized genomic landscape of human breast cancer [5], and iii) Ciriello., *et al*. reported molecular portraits of invasive lobular breast cancer, the second most common breast carcinoma [6]. More and more reports are published day by day on genomic landscapes of cancer drivers, vulnerabilities, drug resistance and metastasis for various types of malignancies.

Definition and classification of many cancer subtypes have, consequently, changed according to novel findings on their molecular genetics: e.g. i) chronic myelogenous leukemia (CML) is defined as a myeloproliferative neoplasm that is consistently associated with the *BCR-ABL1* fusion genes resulted from the specific chromosomal translocation t(9;22) called as the Philadelphia chromosome, ii) Burkitt lymphoma is defined as monomorphic medium-sized aggressive B-cell lymphoma highly frequently associated with translocation involving *c-myc* gene, iii) breast secretory carcinoma, an exceptionally rare variant of breast cancer is defined as a low-grade invasive carcinoma with a solid, microcystic and tubular architecture composed of cells producing secretory material associated with a characteristic translocation t(12;15) creating *ETV6-NTRK3* fusion gene (according to the definitions of the WHO classification). Classification according to

cancer specific mutations is reasonable because targeted therapies against specific oncogenes would be theoretically superior to other currently available non-specific anti-cancer drugs. This is, at least in part, proven by the marked therapeutic effects of imatinib an inhibitor of BCR-ABL tyrosine kinase against CML and anti-HER2 antibody therapy such as herceptin against HER2-enriched type breast cancer. Classification of cancer will continue changing as development of molecular genetics and anti-cancer drugs-especially targeting specific cancer driver molecules.

Considering that morphological classification may be subjective and could be affected by many human factors that are difficult to be standardized, classification by well-organized genetic analyses seem to be more objective, reliable and reproducible. In addition, genetic classification is more accurate because it can be done referring a number of genes (multi-gene analyses): e.g. PAM-50 ROR, Oncotype DX, and MammaPrint for breast cancer. Classical histopathological observation, however, has multiple advantages. Intrinsic subtypes of breast cancer can be also conveniently and rapidly done by immunohistochemistry of 4 surrogate markers including estrogen receptor, progesterone receptor, HER2 and Ki-67 (MIB-1). Histological grading of breast cancer with Nottingham histologic score system, consisting of gland formation, nuclear atypia and mitotic activity, is well correlated with the prognosis. Vessel invasion predicts the potential metastasis of the cancer. Endogenous immune response which can be evaluated by histopathological observation might be related to the prognosis. There are also many hurdles for the realization of correct genetic classification to be overcome. Appropriate genetic analyses can be possible only with samples containing significant proportion or amount of cancer cells while pathologist can distinguish a few cancer cells from millions of normal surrounding cells. Cost of genetic analyses is still much more expensive than histopathological analyses. Moreover, validation of genetic classification cannot be possible without clinical and histological information. Clinical pathology based on morphological observation, therefore, will continue to play important roles in clinical practice, clinical researches and experimental medicine. Considering that technology has resolved many problems that seemed to be impossible, completely automated genetic classification or diagnosis of cancer might be accomplished in the distant future. It should be still noted that the genetic classification will be based on or piled up on the legacy of Dr. Virchow and other pathologists.

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