EDITORIAL

Histiocytic/dendritic cell transformation of indolent B-cell neoplasms: Clinical laboratory evidence of lineage conversion in hematolymphoid malignancies

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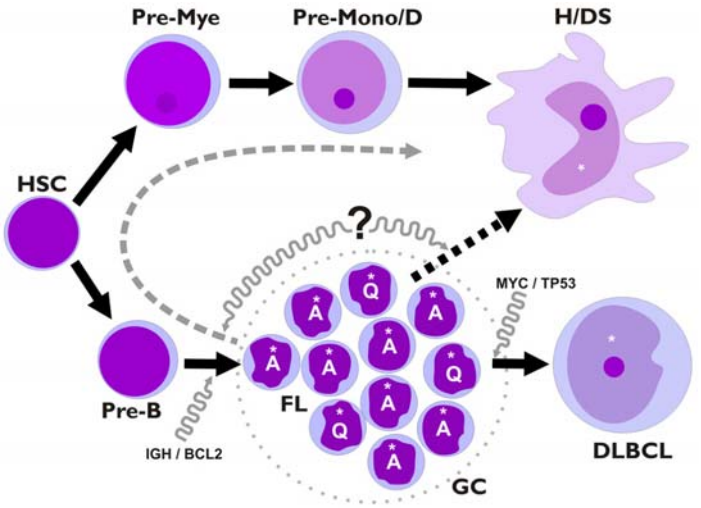
It is well known that pluripotent progenitors of normal hematopoietic cells can differentiate into cell lineages that are distinct in morphology, immunophenotype and biological function [1]. The conventional concept holds that once a hematopoietic progenitor is committed to a given lineage, its fate is sealed and irreversible. This phenomenon of lineage commitment has also been universally observed in hematolymphoid neoplasms in the past. For instance, follicular lymphoma (FL) [2] and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) [3] are fully differentiated indolent B-cell neoplasms and often transform during their prolonged disease course to malignancies with different morphology and more aggressive clinical behavior; however, the secondary neoplasms typically retain the original B-cell lineage immunophenotype. This perception of unidirectional evolution in mature hematolymphoid malignancies has been recently challenged by several clinical studies and in vitro experimental data. A few mature B-cell neoplasms, including FL and CLL/SLL, have been associated with subsequent or concurrent histiocytic/dendritic cell sarcoma (H/DS) [4-12]. The latter neoplastic entity is distinct not only in morphology but also in immunophenotypic profile from the associated B-cell neoplasm. Given the conventional concept, these cases have been thought of as coincidental or two separate neoplasms in the same individual before laboratory diagnostic tests demonstrated genotypic features suggestive of a clonal origin between the primary B-cell neoplasm and secondary H/DS [7-12]. Feldman et al. [7] in their recent article, investigated the clonal relationship between FL and concomitant or secondary H/DS in the same patients and provided for the first time convincing evidence that the two morphologically and immunophenotypically distinct neoplasms share B-cell genotypic identities, suggesting possible "trans-differentiation" of FL into H/DS. Subsequently, histiocytic/dendritic cell transformation has been reported in indolent B-cell neoplasms other than FL by other groups [9-11].

Histiocytic or dendritic cell sarcomas are extremely rare neoplasms derived either from mature phagocyte or other antigen-presenting cells in tissue sites [13, 14]. The diagnoses are based on morphology and immunophenotype per the recent World Health Organization criteria [14]. When H/DS is associated with an indolent B-cell lymphoma, either concurrent or

metachronous, the issue of a clonal relationship with the primary B-cell neoplasm is raised. In this circumstance, the clonal relationship cannot be determined simply by immunophenotyping of the two malignancies because of the lineage conversion in the transformed neoplasm. It has been documented that terminally differentiated hematolymphoid cells can have their morphology and immunophenotype altered after an aggressive transformation, but their basic genotypes are more persistent and typically remain the same. Therefore, the clonal relationship between two distinct hematolymphoid neoplasms, either metachronous or concurrent, in the same individual has been defined by detecting the following genotypic signatures: 1) Identical gene rearrangement products in cases of B-cell or T-cell neoplasms as a primary hematolymphoid malignancy [7-12]; 2) Identical cytogenetic abnormalities or identical stem line changes in cases of primary indolent lymphoid malignancies harboring a specific cytogenetic abnormality [7, 11, 12]. In the former clinical scenario, clonal gene rearrangement products are usually detected by PCR-based assays and amplicons from primary and secondary neoplasms are compared for their size of base pair length. The same size of clonal amplicons from primary and secondary neoplasms are considered to have identical rearrangement of either the IG gene or TCR gene and are defined as sharing a common clonal origin; whereas, different sizes of clonal amplicons or absence of a clonal amplicon in the secondary neoplasm are essentially considered to be clonally unrelated. Ultimately, clonal amplicons from primary and secondary neoplasms can be eluted from an electrophoresis gel and sequenced in order to further confirm the identical breakpoint or segmental use of the gene rearrangement products [7, 9, 11, 12]. In many cases of aggressive transformation, the transformed hematolymphoid neoplasms often contain admixed primary indolent lymphoid neoplasms on histologic sections. Therefore, identical amplicons between primary and secondary neoplasms have to be interpreted with caution because the clonal amplicon may be amplified from the residual primary B-cell clone rather than from H/DS on the section with the predominant latter neoplasm. To avoid this issue, immunohistochemical stains targeted against the B-cell neoplasm are carefully evaluated to ensure the absence of the primary B-cell neoplasm on the tissue section tested for gene rearrangement in the neoplastic cells of H/DS [7, 11, 12]. In addition, the immune-directed laser-captured microdissection (LCM) technique has been applied to collect isolated cells of B-cell leukemia/lymphoma or H/DS before extraction of DNA for gene rearrangement analysis [7, 9]. Ideally, immune-guided cell sorting can provide more targeted analysis, but, owing to the nature of clinical diagnosis and the rarity of the events, fresh tissue is usually unavailable for such a procedure. In the latter clinical scenario, the cytogenetic abnormalities can be detected by conventional karyotyping and Fluorescent In Situ Hybridization (FISH). In most medical institutions in the United States, conventional karyotyping is often not performed on an extramedullary tissue specimen for diagnostic purposes, and thus, fresh tissue is usually not collected unless there is a special indication. However, if a specific cytogenetic abnormality is identified or suggested in the primary lymphoid neoplasm, IGH/BCL2 in FL for instance; FISH with the probe for the fusion gene or other changes can be used on the secondary hematolymphoid neoplasm to determine its clonal identity [7, 9, 11, 12]. FISH analysis can now be performed not only on metaphase cells but also on fresh interphase cells as well as formalin fixed paraffin imbedded tissue blocks. Unlike a PCR-based assay, FISH analysis does not often have an issue of contamination by the primary lymphoid neoplasm because the sections containing pathologically isolated neoplasms can be selected for the assay. For example, a high percentage of IGH/BCL2 fusion on the section with histocytic sarcoma but with no immunohistochemical evidence of B-cell lymphoma would confirm that histiocytic sarcoma harbors the cytogenetic abnormality. Nonetheless, targeted FISH has been used by some investigators to avoid the issue when B-cells are focally present on the sections with H/DS [15]. PCR for the major breakpoint (MBR) of IGH/BCL2 fusion gene has been performed to compare the amplicons from FL to those from H/DS in the same individuals [7], but conclusions should be drawn with caution because of the issue of amplification from residual FL in H/DS.



B-cell precursors acquire t (14; 18) in the bone marrow before migrating to the GC of a lymph node, where the differentiated B-cells with IGH/BCL2 (indicated by asterisks) transform into FL presumably under the effect of other genetic alterations. Clonal evolution follows "cis-pathway" in the majority of cases resulting in DLBCL (solid line), presumably due to additional changes in MYC, TP53 or other genes, while "trans-evolution" could occur in rare cases resulting in H/DS (heavy broken line) or other hematolymphoid neoplasms with an unclear underlying mechanism. The light broken line represents a hypothetical dedifferentiation pathway in lineage conversion. Asterisks in nuclei of H/DS and DLBCL indicate mutated IGH/BCL2 inherited from FL clones.

Figure 1. Schematic representation of clonal evolution of follicular lymphoma

Abbreviation: HSC=hematopoietic stem cell (pleuropotent); Pre-B=B-cell precursor; Pre-Mye=myeloid precursor; Pre-Mono/D=monocytic/dendric precursor; FL=follicular lymphoma; GC=germinal center; H/DS=histiocytic/dendritic cell sarcoma; DLBCL=diffuse large B-cell lymphoma; A=lymphoma cell in active growth; Q=lymphoma cell in quiescent/resting stage

A mature B-cell, such as a neoplastic cell in FL, is more advanced in differentiation and has presumably lost its lineage plasticity. How does it circumvent this restriction and convert to a neoplasm of different lineage? A few possible pathways have been proposed to explain this extraordinary phenotypic conversion, including dedifferentiation, common progenitor, and trans-differentiation mechanisms (Figure 1) [7, 16, 17]. Both dedifferentiation and common progenitor models postulate that neoplastic mature B-cells lack lineage plasticity, and thus, cannot undergo clonal evolution to different lineages directly from a mature neoplastic clone. In the dedifferentiation model [17, 18], this barrier could be bypassed by regressing to the pluripotent progenitor stage and regaining the capability of differentiation along a different pathway, such as to histiocytic or other hematolymphoid lineages. Similarly, in the common progenitor model [7, 17], a premalignant progenitor, particularly a pluripotent progenitor, would be shared by neoplastic B-cells and histiocytic/dendritic cells. In "trans-differentiation"[16,17], a process bypassing the progenitor stage, mature neoplastic B-cells would differentiate directly into phenotypically different hematolymphoid lineages presumably via genetic or epigenetic changes, that are poorly understood at the current time. While altered expression of PAX5 has been suggested to play a pivotal role in this process [7], recent investigation suggests that genes other than PAX5 may be involved in the process as well [10]. Currently, the optimal treatment for H/DS secondary to an indolent B-cell neoplasm remains unknown. We hope that along with elucidation of the molecular mechanism for the lineage conversion in B-cell neoplasms, the neoplastic transformation of not only hematopoietic neoplasms but also other malignancies will be better understood, and therapeutic interventions against transformed neoplasms will be well-targeted.

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