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Review article

Moving from "single gene" concept to "functionally homologous multigene complex": The SWI/SNF paradigm

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> ".There is probably not a gene worth its name whose alteration does not result in a morphologic change", Juan Rosai, MD, The 65th AMR Seminar, comments on Case 1, 2014.

Genetic alterations involving human genes with tumor suppressor properties have emerged over decades as central mechanisms underlying the initiation, development and progression of cancer. Historically, a "single gene=single disease" dogma has been widely adopted to the extent that *SMARCB1* (*INI1*) alterations were considered universally equal to and defining for malignant rhabdoid tumors of the central nervous system. This initially misconceptualized approach made the use of *SMARCB1* genetic testing and the SMARCB1 immunohistochemistry (which has emerged later) almost restricted to the neuropathology practice and related literature.[1] Moreover, the "*INI1-rhabdoid dogma*" has negatively impacted the critical approach to the classical morphology with the consequence of including several distinct entities into the rhabdoid tumor category solely on the basis of their SMARCB1 deficiency.

However, with the recognition of malignant rhabdoid tumors occurring outside the territories of the central nervous system (in particular within soft tissue and kidneys) and the increasing use of SMARCB1 antibodies, the SWI/SNF immunohistochemistry found gradually its way into the general surgical pathology practice and related literature.[2] This intermediate evolutionary phase paved the way to a more deep insight into the rules SMARCB1 plays in other non-rhabdoid neoplastic entities of soft tissue, and later, also of diverse parenchymal or visceral organs. With this new dimension, the historical dogma "*INI1 = rhabdoid*" broke down.[3] Several studied have convincingly illustrated that SMARCB1 loss can represent either a primary (and frequently sole) genetic event driving specific, usually undifferentiated looking, neoplasms (such as malignant rhabdoid tumor and epithelioid sarcoma) ,[3] but can as well be superimposed on well-known preexisting specific genetic pathways in differentiated neoplasms of glial, meningeal, epithelial, and, rarely, mesenchymal origin, thereby heralding a process of "dedifferentiation".[3] However, the old "*single gene*" approach has increasingly failed to explain a rhabdoid cell morphology in many of pure and composite rhabdoid neoplasms, which has led to questioning the specificity of the rhabdoid phenotype in general.[4,5]

However, lessons learned from other diseases (in particular mismatch repair deficiency in colorectal cancer and the succinate dehydrogenase "SDH" complex pathway in hereditary paraganglioma syndromes) have nicely illustrated that a "*functionally homologous multigene complex*", rather than the old "*single gene concept*" can reliably and effectively identify a variety of neoplasms lacking the prototypical gene mutation expected for their morphology. Indeed, this emerging "*multigene complex paradigm*" enabled us to better understand and explain the SWI/SNF-typical phenotype in several neoplasms occurring in different organs and displaying in general a striking morphological homology, irrespective of their exact histogenetic origin and the specific SWI/SNF subunit affected by the mutation. Parallel to these recent developments in diagnostics, the SWI/SNF complex has evolved from its original canonical 5-genes structure to encompass now >20 genes mapped to different chromosomes and chromosomal regions.[6,7] The consequence of the many genetic- and morphology/phenotype-guided studies was a revolutionary refinement of the taxonomy of many visceral and soft tissue neoplastic entities. Moreover, our better understanding of the diversity of the SWI/SNF variants assembled differentially in the progenitor cells and stem cells of different organs might shed more light on the striking site-specific clustering of mutations in certain SWI/SNF genes affecting neoplasms of specific organs.[8]

Notably, the ever increasing use of emerging SWI/SNF immunohistochemistry in daily surgical pathology practice has eliminated not only the old dogma "*rhabdoid means INI1* and vice versa", but other general misperceptions such as "*SWI/SNF = aggressiveness or malignancy*" and "*SWI/SNF = rhabdoid*" as well. The central role this intriguing genetic pathway plays in several frequently aggressive malignancies has promoted the initiation of extensive clinical research studies looking for potential therapeutic opportunities to target the SWI/SNF complex collapse. Promising results underline the need for recognition and appropriate classification of the SWI/SNF-driven neoplasms in routine practice.[9-11] Finally, correct recognition of SWI/SNF-related neoplasms positively enhances identification of potential hereditary cases.[12] Establishment of the SWI/SNF deficiency as a defining criterion for several old and new entities (e.g. SMARCB1 loss in epithelioid sarcoma, and SMARCA4 loss in small cell carcinoma of the ovary, hypercalcemic type and in SMARCA4-deficient undifferentiated intrathoracic tumors) represents a landmark and underlines the need for including these new and emerging "next generation immunoantibodies" in routine surgical

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pathology practice. This special issue of the *Seminars* is devoted to selected topics related to SWI/SNF-deficient neoplasms encountered routinely by surgical pathologists.

Declaration of Competing Interest

None.

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