SWI/SNF complex, promising target in melanoma therapy

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Abstract

Therapeutic strategies based on epigenetic regulators are rapidly increasing in light of recent advances in discovering the role of epigenetic factors in response and sensitivity to therapy. Although loss-of-function mutations in genes encoding the SWItch/Sucrose NonFermentable (SWI/SNF) subunits play an important role in the occurrence of approximately 34% of melanomas, the potential of using inhibitors and synthetic lethality interactions between key subunits of the complex that play an important role in melanoma progression must be considered. A theme developed from recent studies showed the crucial role of the SWI/SNF complex in defining the therapeutic efficacy of melanoma. In light of accumulated data, ARID2, ARID1B, SMARCA4 (BRG1) and SMARCA2 (BRM) have the most important mutations in melanoma. Considering the important role of epigenetic players in immune therapy resistance in a patient with melanoma, It is crucial to determine how SWI/SNF complex can contribute to melanoma therapy through different subunits. Combinational therapy and synthetic lethality approaches are the well-studied most current findings that show promising clinical responses in melanoma. Of note, further investigations need to be done to elucidate the context-dependent behavior of SWI/SNF subunits, possible off-target inhibition, immunosuppression, and the chance of relapse in target therapy for melanoma. Targeting the druggable SWI/SNF bromodomains (BRD7, BRD9, SMARCA4, SMARCA2), using the BET inhibitors as long as the HDAC inhibitors and identification of synthetic lethal interactions involved in melanoma such as SMARCA4 and ARID2 presents an additional possibility for novel strategies targeting the SWI/SNF subunits toward precise medicine of melanoma. Given the significant role of the SWI/SNF complex in melanoma, future therapeutic approaches must focus on mechanisms of synergic effect and synthetic lethality to enhance the therapeutic benefits of inhibitors, particularly when there is a deficiency in the functional domains mentioned above. We strongly believe an understanding of potential therapeutic vulnerabilities based on SWI/SNF in melanoma is leading to personalized and targeted cures and open up new areas of clinical investigations.