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Autore Yoshimasa Saito

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Studies have shown that alterations of epigenetics and microRNAs (miRNAs) play critical roles in the initiation and progression of human cancer. Epigenetic silencing of tumor suppressor genes in cancer cells is generally mediated by DNA hypermethylation of CpG island promoter and histone modification such as methylation of histone H3 lysine 9 (H3K9) and tri-methylation of H3K27. MiRNAs are small non-coding RNAs that regulate expression of various target genes. Specific miRNAs are aberrantly expressed and play roles as tumor suppressors or oncogenes during carcinogenesis. Important tumor suppressor miRNAs are silenced by epigenetic alterations, resulting in activation of target oncogenes in human malignancies. Stem cells have the ability to perpetuate themselves through self-renewal and to generate mature cells of various tissues through differentiation. Accumulating evidence suggests that a subpopulation of cancer cells with distinct stem-like properties is responsible for tumor initiation, invasive growth, and metastasis formation, which is defined as cancer stem cells. Cancer stem cells are considered to be resistant to conventional chemotherapy and radiation therapy, suggesting that these cells are important targets of cancer therapy. DNA methylation, histone modification and miRNAs may be deeply involved in stem-like properties in cancer cells. Restoring the expression of tumor suppressor genes and miRNAs by chromatin modifying drugs may be a promising therapeutic approach for cancer stem cells. In this research topic, we discuss about alterations of epigenetics and miRNAs in cancer and cancer stem cell and understand the molecular mechanism underlying the formation of cancer stem cell, which may provide a novel insight for treatment of refractory cancer.