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Influence of stemness inhibitors on the immunomodulatory properties of colorectal cancer

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Abstract

Colorectal cancer (CRC) is a heterogeneous disease characterized by a diverse tumor microenvironment comprising immune and non-immune components. Acquired mutations and phenotypic plasticity in the tumor microenvironment create a diversity of cells whose interactions contribute to tumor progression and create resistance to anticancer therapy through various activated mechanisms. At the molecular level, four subtypes of colorectal cancer (CMS1-4) have been validated, differing in their aggressive characteristics and immune infiltration. With the rapid development of oncology science and the development of new cancer treatment strategies, more attention is given to the microenvironment surrounding cancer cells. Since the tumor is densely infiltrated by host immune cells, especially macrophages, it could be a promising target for developing new treatment strategies. This study aims to explore how inhibition of CRC cell stemness properties with specific inhibitors could modulate macrophage polarization, shifting the immune balance from protumoral M2 type to the antitumoral M1 type. We evaluated the effect of four stemness inhibitors - salinomycin, SB-431542, JIB-04, and napabucasin - on CMS4 CRC cell lines (HCT116 and SW620) and human peripheral blood-derived macrophages in an indirect co-culture model. Our results demonstrate that CMS4 CRC cell lines induced distinct macrophage polarization patterns, with HCT116 promoting M2 macrophages and SW620 leaning toward M1 profile. The combination of stemness inhibitors reduced stemness markers (CD133, CD44) in colorectal cancer cells and shifted macrophage polarization toward an M1 phenotype, particularly in co-culture with HCT116. These findings suggest that stemness inhibitors not only target cancer cells but also modulate the immune microenvironment by reprogramming macrophages.
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