

self-renewal and tumorigenicity [113]. These findings suggest that miRNAs may regulate these GCSC properties through EMT induction. Multidrug resistance (MDR) is also a characteristic of CSCs. Previous studies have shown that miR-15b and miR-16 may play roles in the development of MDR in GC cells by targeting BCL2, while miR-106a may promote MDR in GC cells by targeting RUNX3 [114, 115]. Shang et al. [116] recently used high-throughput functional screening to identify 11 candidate miRNAs that regulated MDR in GC, and found that among these miRNAs, miR-508-5p reversed MDR most efficiently by targeting ABCB1 and zinc ribbon-domain-containing 1.

Kong et al., revealed that inflammation could affect miRNA expression, and that down-regulation of the tumor suppressor miR-7 represented a novel mechanism whereby the inflammatory response promoted gastric tumorigenesis in K19-C2mE and K19-Wnt1/C2mE mouse models [117]. We revealed that infiltrated macrophages in the tumor microenvironment may contribute to redox adaptation through CD44 up-regulation by miR-328 suppression [118]. Sugihara et al. [119] found that TAMs down-regulated miR-30e*, which suppressed Bmi1 expression by targeting the Bmi1 3'UTR in GCs. These findings suggest that inflammation and stromal cells in the tumor microenvironment are deeply implicated in the regulation of miRNA expression in GC cells. Some miRNAs are down-regulated in GC by methylation of the CpG islands in their promoters [120]. However, many factors can affect miRNA expression, and although the methylation of CpG islands is one of these factors, the mechanisms of miRNA methylation remain largely unknown. Further studies are, therefore, needed to determine the pivotal factors affecting miRNA expression in GC cells.

Future perspectives

Solid tumors are known to exhibit hierarchical organization involving CSCs and non-CSCs. However, a recent study has indicated that this hierarchy may be reversible through epigenetic gene regulation [121], suggesting that therapeutic strategies targeting CSCs themselves might be insufficient to exterminate cancer cells. Numerous lines of evidence presented in this review indicate that the tumor microenvironment surrounding GCSCs plays a critical role in maintaining the properties of GCSCs. Targeting the unique molecules in the tumor microenvironment and their signaling interactions may, thus, be a promising therapeutic strategy, and may provide a complementary approach to conventional therapies targeting the malignant cells themselves. Further understanding of the precise molecular mechanisms regulating cancer-stromal cell interactions may lead to the development of novel treatment strategies for patients with GC.

Conflict of interest The authors declare that they have no conflict of interest.

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