# The expression of hematopoietic progenitor cell antigen CD34 is regulated by DNA methylation in a site-dependent manner in gastrointestinal stromal tumours

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### ****Abstract****

The anatomic site-dependent expression of hematopoietic progenitor cell antigen CD34 is a feature of gastrointestinal stromal tumours (GISTs). The basis for the differential CD34 expression is only incompletely understood. This study aimed at understanding the regulation of CD34 in GISTs and clarification of its site-dependent expression. Two sample sets of primary GISTs were interrogated including 52 fresh-frozen and 134 paraffin-embedded and formalin-fixed specimens. DNA methylation analysis was performed by HumanMethylation450 BeadChip array in three cell lines derived from gastric and intestinal GISTs, and differentially methylated CpG sites were established upstream of CD34. The methylation degree was further quantified by pyrosequencing, and inverse correlation with CD34 mRNA and protein abundance was revealed. The gene's expression could be activated upon induction of DNA hypomethylation with 5-aza-2'-deoxycytidine in GIST-T1 cells. In patient samples, a strong inverse correlation of DNA methylation degree with immunohistochemically evaluated CD34 expression was documented. Both CD34 expression and DNA methylation levels were specific to the tumours' anatomic location and mutation status. A constant decrease in methylation levels was observed ranging from almost 100% hypermethylation in intestinal GISTs from duodenum to hypomethylation in rectum. CD34 was heavily methylated in gastric PDGFRA-mutant GISTs in comparison to hypomethylated KIT-mutant counterparts. Next to CD34 hypermethylation, miR-665 was predicted and experimentally confirmed to target CD34 mRNA in GIST-T1 cells. Our results suggest that CD34 expression in GISTs may undergo a complex control by DNA methylation and miR-665. Differential methylation and expression of CD34 in GISTs along the gastrointestinal tract axis and in tumours that harbour different gain-of-function mutations suggest the origin from different cell populations in the gastrointestinal tract.

**KEYWORDS:**

CD34; DNA methylation; GISTs; epigenetic regulation

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