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Mapping GWAS variants to endothelial differentiation gene regulatory program uncovers the significance of endothelial cells in complex human diseases

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Endothelial cells are essential components of the vascular system, forming a complex network that supplies vital nutrients to organs throughout the body. Dysfunction in these cells can significantly affect organ functions and is linked to a range of complex human diseases. Notably, the gene regulatory programs active during the endothelial cell differentiation may play a crucial role in disease associations, a relationship that has yet to be thoroughly explored. In this study, we systematically investigated the connection between endothelial gene regulatory programs and genome-wide association studies (GWAS) related to various human diseases and traits. By integrating epigenomic information (specifically H3K27ac ChIP-seq) and long-range chromatin interactions during endothelial differentiation at high temporal resolution, we quantified the correlation between endothelial differentiation stages and human diseases and traits. Our results reveal that while many hematological traits are associated with endothelial differentiation, several complex diseases, including colorectal cancer (CRC) and Alzheimer's disease, show unexpected connections. Notably, CRC exhibits the strongest correlation with late-stage endothelial differentiation, suggesting a significant role for this regulatory program in the development of tumor-associated endothelial cells. These findings highlight the importance of distinct gene regulatory programs in understanding endothelial dysfunction and its implications for various diseases. This comprehensive approach not only deepens our understanding of endothelial biology but also offers insights into potential therapeutic targets for disease management.