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Unraveling the mechanisms of PD1 regulation in Sezary syndrome: Epigenetic regulation as potential mechanism?

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COMMENTARY

In this issue of *JID* Najidh et al. expanded our understanding of PD1 regulation in Sezary syndrome (SS) (Najidh et al., 2023) demonstrating an inverse correlation between DNA methylation status of *PDCD1* gene promotor and *PDCD1* gene and PD1 protein expression that strongly indicates a role for DNA methylation in regulating *PDCD1* gene expression.

PD1 IS EXPRESSED BY TUMOR CELLS FROM SÉZARY SYNDROME

SS is the erythrodermic and leukemic variant within the cutaneous T cell lymphoma (CTCL) spectrum characterized by specific phenotypic and molecular aberrations, affecting tumor growth and dissemination. PD1 is commonly overexpressed by tumor cells of SS that contributed to improved diagnosis and detection by immunohistochemistry or flow cytometry (Cetinozman et al., 2012, Lewis et al., 2022). Moreover, PD1 inhibits T cell activation in the CTCL microenvironment and by binding to PD-L1 modulates disease growth and progression by downregulating anti-tumor responses (Han et al., 2023). Hence, checkpoint blockade has emerged as a highly promising treatment strategy via modulation of tumor cell-immune cell interactions with remarkable tumor responses, albeit only in a subset of patients (Khodadoust et al., 2020). The underlying mechanisms for treatment response and resistance are not completely elucidated. Overall, advanced stages of mycosis fungoides (MF)/SS have a poor prognosis with an estimated 5-year survival of approximately 20 - 60% (Mourad and Gniadecki, 2020).

DYSREGULATION OF THE EPIGENOME IS A HALLMARK OF CTCL

Epigenetic changes such as DNA methylation are known to alter gene expression of oncogenes and tumor suppressors contributing to malignant transformation and tumor phenotype (Baylin and Jones, 2016). In addition, epigenetic changes of genes particularly involved in DNA repair, and cell cycle checkpoint genes have been shown to influence

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cancer chemotherapy responses via signaling pathway alterations. Various molecular mechanisms including transcriptomic and epigenomic regulation have been recognized to drive PD1 expression during acute and chronic antigenic stimuli, and anti-tumors responses. Both high aberrant DNA hyper- and hypomethylation signatures have also been observed in CTCL that are indicative of the specific role of epigenetics in the CTCL pathogenesis (Choi et al., 2015). CTCL cells demonstrated widespread hypermethylation of CpG islands in promotor regions of tumor suppressor gene CDKN2A and recurrent loss of function mutations in epigenetic regulators such as DNMT3A (Kiel et al., 2015, van Doorn et al., 2016).

EPIGENETIC REGULATION OF PD1 IN SÉZARY SYNDROME

To this end, Najidh et al. performed combined analyses of DNA methylation, gene, and protein expression in a large cohort of SS patients (n=38), patients with benign erythroderma (BE; n=10) and healthy controls (HC; n=4) (Najidh et al., 2023). Qualitative assessment of the DNA methylation status of the gene promoter locus *PDCD1* in CD4+ T cells from peripheral blood samples revealed a markedly hypomethylated promotor in SS samples compared to methylated promotor in BE/HC samples. In addition, the authors found a consistent inverse correlation between *PDCD1* gene promoter methylation, *PDCD1* gene expression, and PD1 membranous protein expression. *PDCD1* promoter mRNA and protein levels among SS samples with hypomethylated gene promoters demonstrated a significantly higher expression when compared to methylated gene promoters from SS or BE samples. Furthermore, the authors could show the reversible character of *PDCD1* methylation with low PD1 protein expression on circulating immunophenotypically aberrant CD4+ T cells in 2 follow-up peripheral blood samples.

PD1 AS IMPORTANT THERAPEUTIC TARGET IN SÉZARY SYNDROME

Immune checkpoints are important targets for immunotherapies. However, knowledge on the epigenetic modification of immune checkpoint genes is sparse. Pembrolizumab demonstrated efficacy in inducing anti-tumor responses in a subset of patients with advanced MF/SS (Khodadoust et al., 2020). Notably, a transient worsening of erythroderma in SS patients correlated with high PD1 expression on circulating Sezary cells that did not associate with subsequent clinical responses. Najidh et al. emphasized the need to utilize PD1 checkpoint blockade in combination with therapeutic strategies that involve direct targeting of epigenetic alterations to augment anti-tumor responses (Najidh et al., 2023). Considerations are given to the histone deacetylase inhibitors (HDACi) romidepsin and vorinostat that were approved by the FDA and are currently utilized for CTCL (Lopez et al., 2018). Their efficacies and epigenetic drug effects on DNA methylation and histone deacetylation are well-studied, albeit its effects on the PD1/PD-L1 axis is not known.

Although Najidh et al. have identified epigenetic alterations of PD1 in SS and convincingly demonstrated that these alterations correlated with high *PDCD1* mRNA and PD1 protein expression (Najidh et al., 2023), PD1 regulation is likely to be much more complex, because PD1 is not only expressed on CTCL cells, but on other immune cells in the CTCL tumor microenvironment (TME) and targeting PD1 can have immunomodulatory effects.

In addition to providing an understanding of which active immune TME components may induce and be affected by PD1 function, knowledge of other molecular mechanisms such as transcription factors or other epigenetic parameters in regulating PD1 may help tailor future immunotherapies. miRNAs have been shown to regulate immune checkpoint expression in MF that may be driven by the TME (Han et al., 2022) but is not known for SS. Nevertheless, epigenetic abnormalities in SS may have diverse implications, because they may be heritable and do not only affect gene transcription but regulating cell reprogramming. Larger data sets are needed to validate the predictive value of DNA methylation status of PD1.

CONFLICT OF INTEREST

Advisory board/steering committee: Kyowa Kirin, Helsinn, Citius Pharm; investigator: Kyowa Kirin, Bristol Myers Squibb, Sorrento, Helsinn; research grants: Helsinn, Celgene

Biography

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Clinical Implications:

- PD1 is expressed by tumor cells from Sézary syndrome distinct from benign erythrodermas.
- The inverse correlation between DNA methylation and PD1 expression indicates a role for epigenetic control of *PDCD1* gene expression.
- The DNA methylation status of PD1 may serve as biomarker for response and resistance.

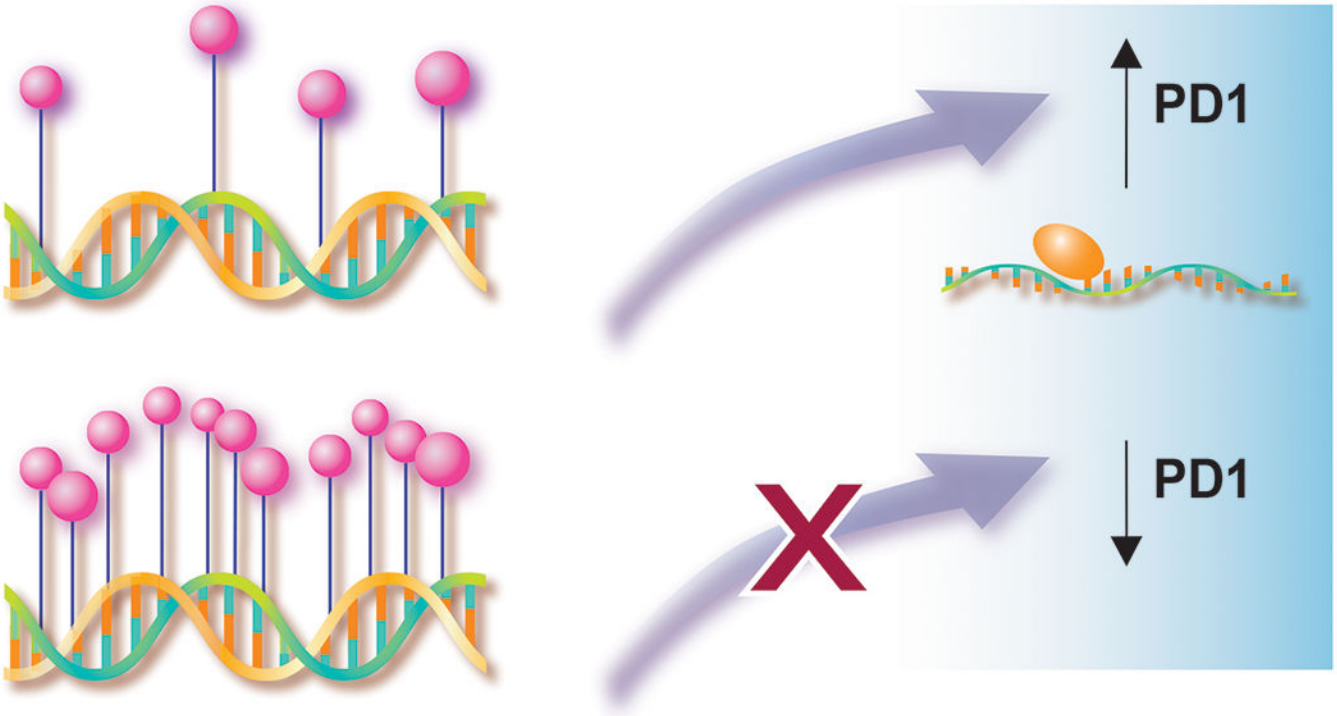

Figure 1:

Inverse correlation of DNA methylation status of PDCD1 gene promotor region and PD1 mRNA and protein expression

Illustration assistance provided by Jan Ruvido Stebbins, Ruvido Medical Illustration, Dexter, MI.