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DNMT1 is expressed in actively-proliferating lymphoid blast cells and significantly associated with E2F gene set in malignancies

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Abstract

DNA methyltransferase 1 (DNMT1) is a maintenance methyltransferase crucial for cellular proliferation and cell cycle activation. DNMT1 is required for the formation of follicular germinal centre (GC) structure and B-cell differentiation into plasma cells. However, little is known on the expression profile and functions of DNMT1 in B cells residing in the non-GC areas of interfollicular regions. In this study, utilising a validated anti-DNMT1 monoclonal antibody (clone 2B5), we demonstrated that in all human lymphoid tissues investigated, DNMT1 was negative in plasma cells but highly expressed in centroblasts residing in the GC region with a number of DNMT1-positive cells residing in the non-GC interfollicular regions. We hypothesised that these cells might be immunoblasts, a type of lymphoid cells that directly transform into plasma cells independent of the GC structure, due to its cellular features *i.e.* large cells containing round nucleus and large nucleolus. Thus, we proceeded to investigate whether the following immune cells in the interfollicular non-GC regions expressed DNMT1 through double immunostaining: T cells ($CD3^+$), immunoblasts ($CD30^+$), natural killer cells ($CD56^+$), macrophages ($CD68^+$) and plasma cells ($CD138^+$). DNMT1 was absent in all these populations except $CD30^+$ immunoblasts. We have previously shown that DNMT1 was frequently expressed in diffuse large B-cell lymphoma (DLBCL), whose cellular origin was thought to arise from mature B cells (*e.g.* centroblasts, immunoblasts, plasma cells), and associated with high Ki-67 (proliferation marker) expression. Both centroblast and immunoblast cell populations are actively proliferating cells. To elucidate these fundamental roles of DNMT1 further (*i.e.* proliferation and cell cycle activation), we examined *DNMT1* transcript expression profile in 31 different types of cancers where it was most highly expressed in DLBCL followed by other malignancies. We subsequently performed Gene Set Enrichment Analysis (GSEA) on the top 15 cancers with the highest *DNMT1* transcript values, and showed that the "E2F targets" gene set involved in cell cycle activation were most significantly enriched ($p<0.05$; FDR<0.01) in all 15 cancer types. Taken together, these suggest that the fundamental roles of DNMT1 in cellular proliferation and cell cycle activation occur in both normal and malignant cell types.

Keywords: DNMT1; immunoblast; diffuse large B-cell lymphoma; proliferation; cell cycle

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