RIF1 acts as a cell identity gatekeeper during mature B cell differentiation

Rahjouei A.[1*], Kabrani E.[1*], Berruezo-Llacuna M.[1], Altwasser R.[1], Delgado-Benito V.[1], Keller L.[1], and Di Virgilio M.[1,2,]

[1]Laboratory of Genome Diversification and Integrity, Max Delbrück Center for Molecular Medicine in the Helmholtz Association, Berlin 13125, Germany;

[2]Charité-Universitätsmedizin Berlin, Berlin 10117, Germany; Mailing address: michela.divirgilio@mdc-berlin.de

*These authors contributed equally

Abstract

Upon antigenic challenge, mature B lymphocytes form distinct anatomic structures in secondary lymphoid organs called germinal centers (GC). Slightly before entry into the GC, cells diversify their B cell receptor (BCR) through the process of class switch recombination (CSR), while later in the GC reaction they increase their BCR-antigen affinity through somatic hypermutation (SHM). Eventually, GC B cells differentiate into memory cells or antibody secreting cells called plasma cells (PC).

RAP1-interracting factor (RIF1) was initially described in yeast where it contributes to telomeric length maintenance. In mammalian cells though, RIF1 does not act as a regulator of telomere homeostasis but plays multiple roles in the preservation of genome integrity during DNA replication and repair. In B cells, RIF1 ability to protect DNA double-strand break (DSB) ends against resection promotes productive repair of programmed breaks generated during CSR. While germline RIF1 knockout mice exhibit embryonic lethality, deletion of RIF1 in embryonic stem cells destabilizes their pluripotency. Interestingly, during B cell development, RIF1 expression levels are dynamically regulated. This observation led us to evaluate whether RIF1 plays an additional role during late B cell differentiation, apart from its classical contribution to CSR through DNA repair. We found that RIF1 expression is robustly upregulated immediately after B cell activation. Interestingly, *ex vivo* activated *Rif1*$^{fl/fl}$ *Cd19*$^{Cre/+}$ mouse B cells showed a deregulated expression profile enriched in genes normally expressed in plasma cells. In addition, RIF1 ablation resulted in an accelerated plasma cell-like phenotype *ex vivo.* Altogether, our data support a model where RIF1 modulates PC differentiation by acting as a B cell identity gatekeeper during the GC reaction.