

*Structural Studies on an Atypical Rho GTPase RhoH*

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Rho GTPases acts as bio molecular switches by shuttling between GTP bound active ('ON') state and GDP bound inactive ('OFF') state to regulate many important biological processes like cell proliferation, actin reorganization and cell migration. They have conserved regions like, G-domain, Switch 1 and Switch 2 and a 13 amino acid Rho specific insert domain [1].

RhoH is a constitutively active 'atypical' Rho GTPase expressed only by the hematopoietic cells. Sequence divergence in the switch 2 region and the phosphate binding loop have resulted in loss of GTPase activity of RhoH, rendering it to be constitutively active. It also exhibits other atypical features such as a unique Carboxyl terminal insert domain and a shorter 7 amino acid Rho specific insert. RhoH is involved in cell migration and is also implicated in different types of lymphomas [2]. It regulates T-cell receptor (TCR) signalling by promoting localization of Zap70 at the TCR [3]. Furthermore, RhoH is known to act as a negative regulator of a typical Rho GTPase- Rac1 for processes such as cell proliferation, survival and migration [1, 2]. Despite nearly two decades of study, the regulation and switching mechanism of RhoH remains still elusive.

In order to gain mechanistic insights on RhoH, it is being expressed in a heterologous system and attempts are underway to crystallize the protein. Attempts are also being made to co-express RhoH with Zap 70 in a eukaryotic expression system to elucidate the structural basis of their interaction. Using X-ray crystallography, we aim to understand the structure of RhoH in its apo form and its complex with Zap70. Comparison of the RhoH structure with the already elucidated structures of the typical Rho GTPases like RhoA and Rac1 will help improve our understanding about the regulation of RhoH and also help delineate the significance of other atypical features of RhoH. As RhoH is the only Rho GTPase with opposing role to Rac1, it is a potential anti-metastatic therapeutic target for leukemia. The structure of RhoH-Zap70 complex will provide insight to initiation of TCR signalling which is crucial for determining the cell fate.

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