Chaetoglobosin A preferentially induces apoptosis in chronic lymphocytic leukemia cells by targeting the cytoskeleton

Chronic lymphocytic leukemia (CLL) is an incurable malignancy of mature B cells. One of the major challenges in treatment of CLL is the achievement of a complete remission to prevent relapse of disease originating from cells within lymphoid tissues and subsequent chemoresistance. In search for novel drugs that target CLL cells also in protective microenvironments, we performed a fungal extract screen using cocultures of primary CLL cells with bone marrow-derived stromal cells. A metabolite produced by Penicillium aquamarinium was identified as Chaetoglobosin A, a member of the cytochalasan family that showed preferential induction of apoptosis in CLL cells, even under culture conditions that mimic lymphoid tissues. In vitro testing of 89 CLL cases revealed effective targeting of CLL cells by Chaetoglobosin A, independent of bad prognosis characteristics, like 17p deletion or TP53 mutation. To provide insight into its mechanism of action, we showed that ChA targets filamentous actin in CLL cells and thereby induces cell cycle arrest and inhibits membrane ruffling and cell migration. Our data further revealed that Chaetoglobosin A prevents CLL cell activation and sensitizes them for treatment with PI3K and BTK inhibitors, suggesting this compound as a novel potential drug for CLL.

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