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Targeting early B-cell receptor signaling inducesapoptosis in leukemic mantle cell lymphoma

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Abstract

Mantle cell lymphoma (MCL) is an aggressive and incurable malignant lymphoma, representing approximately 5% of non-Hodgkin lymphomas (NHL).We previously showed that B-cell receptor (BCR) signaling pathways are important forin vitro survival of mantle cell lymphoma (MCL) cells. To further identify early BCRactivated signaling pathways involved in MCL cell survival, we focused our study onBCR-proximal kinases such as LYN whose dysregulations could contribute to the aggressive course of MCL. We showed that LYN was constitutively phosphorylated in MCL cell line (HBL-2) and in 9/10 leukemic MCL cases. Blocking LYN activity with the specific inhibitor PP2 or with dasatinib suppressed constitutive LYN activation and increased in vitro spontaneous apoptosis of primary MCL cells. BCR engagement resulted in an increase of LYN phosphorylation leading to activation of c-JUN NH2-terminal kinase (JNK) and over-expression of the early growth response gene-1 (EGR-1). Specific inhibition of JNK with SP600125 reduced level of basal and BCR-induced expression of EGR-1 positioning EGR1 as a JNK downstream target. Treatment with PP2 or with dasatinib suppressed BCR-induced LYN activation and was associated with an inhibition of both JNK phosphorylation and EGR-1 expression. Inhibition of LYN or JNK activity by their respective inhibitors suppressed BCR-induced MCL cell survival in all cases analysed. This study highlights the importance of proximal BCR signaling in MCL cell survival and points out to the efficiency of LYN inhibitors in suppressing early BCR signaling events and in inducing apoptosis.

Biography

Mohand-Akli BOUKHIAR has completed his PhD degree in Molecular and cellular Biology in December 2011 from Paris 13 University. During 2012, he worked as a young researcher at Paris 13 University and he is currently preparing an interuniversity diploma in drug clinical trial at Paris 6 University.