The Crucial role of Mg^{2+} in conformational change of KRas

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KRas proteins plays an important role in various cellular events such as cell proliferation, differentiation, and survival[1]. KRas mutations impair both the intrinsic and GAP stimulated GTP hydrolysis activity[2], leading to hyperactivation of KRas signaling and ultimately cancer. As one of the important Ras cofactors, Mg^{2+} is coordinated in an octahedral arrangement with a high affinity on Ras proteins[3]. Mg^{2+} has been established essential for both guanine nucleotide binding and GTP-hydrolysis of Ras proteins. For instance, in HRas the difference in affinity between HRas and guanine nucleotide in the presence or absence of Mg^{2+} is ~500-fold[4]. However, HRas is rarely mutated in human cancers with ~10% rate found in only bladder and cervical cancers[5]. The mechanism of Mg^{2+} interaction with the most prevalent and oncogenic KRas has never been investigated yet. Herein, through long-time scale molecular dynamics simulations at all-atom level, we revealed that cofactor Mg^{2+} plays a crucial role in the conformational changes of KRas. The mutation of GLY12 on KRas, G12D, triggers a distinct shift in the interaction patterns between Mg^{2+} and KRas, makes the conformation of KRas(G12D) is more stable compared to wild-type and KRas(G12C) (Figure 1 and Figure 2).

REFERENCES

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FIGURES

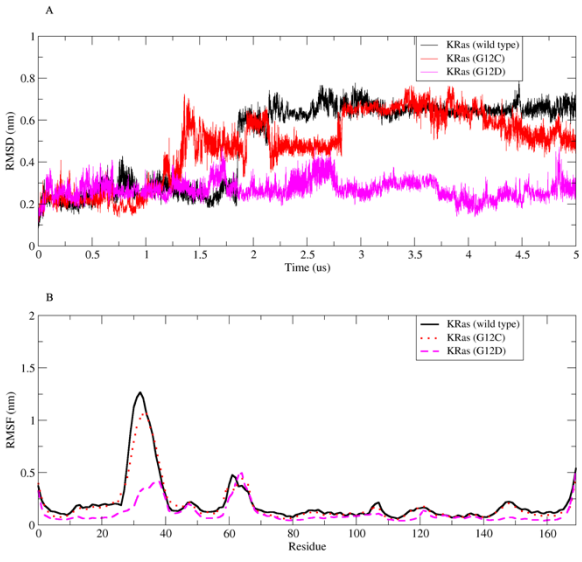

Figure 1: RMSD and RMSF information of different KRas conformational changes

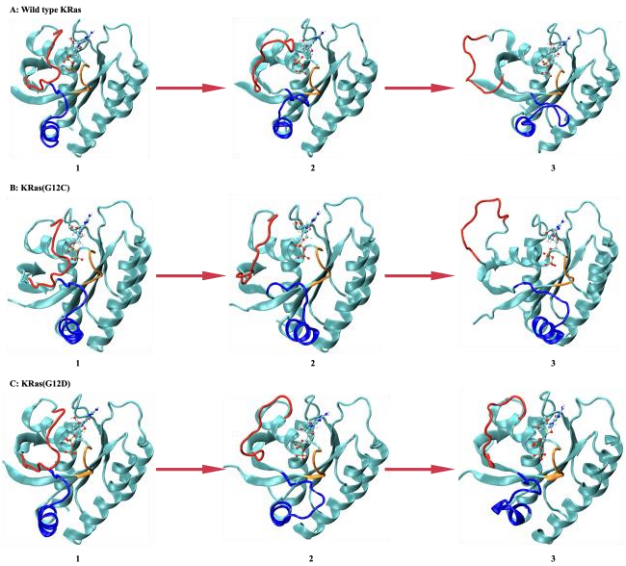

Figure 2: Selected snapshot of different KRas conformational changes