

# Revisiting the mechanism of membrane anchoring of the HIV-1 matrix protein by a molecular modelling approach

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During HIV assembly in infected host cells, the interaction of the *N*-terminus Matrix (MA) domain of the viral Gag protein with the plasma membrane lipid PI(4,5)P2 appears as the first crucial step for particle assembly. This model is reinforced by recent lipidomic analysis of the viral envelop, showing an enrichment in PI(4,5)P2.<sup>[1]</sup> It was previously suggested that this anchoring might require a 'Myristoyl switch' i.e. the PI(4,5)P2 binding to MA occurs in an allosteric site that could promote Myristate exposure.<sup>[2]</sup> It was also shown that the 2'-acyl chain (usually unsaturated) was able to flip into an hydrophobic pocket of MA, allowing therefore the complex to partition into pre-existing lipid microdomains, namely rafts.<sup>[2]</sup>

Starting with the NMR structure of the Myristoylated HIV-1 MA protein, we performed multiple coarse grained molecular dynamics simulations to simulate the anchoring of the HIV-1 MA protein to a PI(4,5)P2 containing membrane model. Quite surprisingly, it was observed that the Myristoyl group could easily unbind from its initial hydrophobic pocket in MA thus allowing spontaneous anchoring of the protein to the membrane. More importantly, it was observed that after having found a stable orientation, the protein was able to confine PI(4,5)P2 all around its molecular surface with a preferential binding site in the same regions as that described by NMR data. But, on the contrary to what NMR showed, no flipping of the 2'-acyl chain of the PI(4,5)P2 was observed. The acyl chains stayed within the hydrophobic core of the lipid membrane. Our model therefore suggested that the protein itself, after membrane anchoring, could be able to confine PI(4,5)P2, without any requirement of pre-existing domains, as suggested in Kerviel *et al.*<sup>[3]</sup> Moreover, our estimation of the required energetic cost for myristoyl release suggested that no Myristoyl switch mechanism would be necessary.<sup>[4]</sup>

## References

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