The pH-dependent membrane crossing mechanism of Lewis bases antitumor drugs

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Targeted cancer therapeutics remains a central goal of cancer research. The tumor microenvironment (TME) is an important component of tumor development that influences several key processes such as tumor cell phenotype, proliferation, immune evasion, and drug resistance [1]. An important feature of the TME is the increased acidity of the extracellular milieu (pH 6.0-6.8), generated by enhanced anaerobic glycolysis coupled with higher levels of proton extrusion via upregulated proton pumps. This process creates a pH gradient between the extracellular and intracellular environments, potentially creating a barrier for hydrophobic Lewis base drugs to enter the cells. The high pK_a values (7.5-10) of these compounds including for example some tyrosine kinase inhibitors like sunitinib and nintedanib, require them to first undergo deprotonation before passively diffusing through the plasma membrane into the cells, which becomes more difficult in acidic microenvironments like the TME. This study aims at investigating the pH-dependent membrane insertion mechanism of several Lewis base drugs. We performed pH replica-exchange (pHRE) [2] simulations of sunitinib and nintedanib and a few other compounds, interacting with a phosphatidylcholine lipid membrane. We calculated pK_a profiles for all these systems, which capture the desolvation effect along the membrane normal [3]. Based on our data, we can also follow the average protonation and relative distribution between water and lipid phases at a given pH value. The obtained pK_a and protonation profiles along the membrane insertion pathway can help us interpret the available experimental data on how some of these compounds struggle to insert into tumor cells whereas other hydrophobic weak base drugs are highly sequestered within lysosomes [4].

References

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Acknowledgment

This work was supported by the European Cooperation in Science and Technology (COST Action CA17104) and FCT, Portugal (UIDB/04046/2020 and UIDP/04046/2020).