Targeting a ruthenium complex to the nucleus with short peptides

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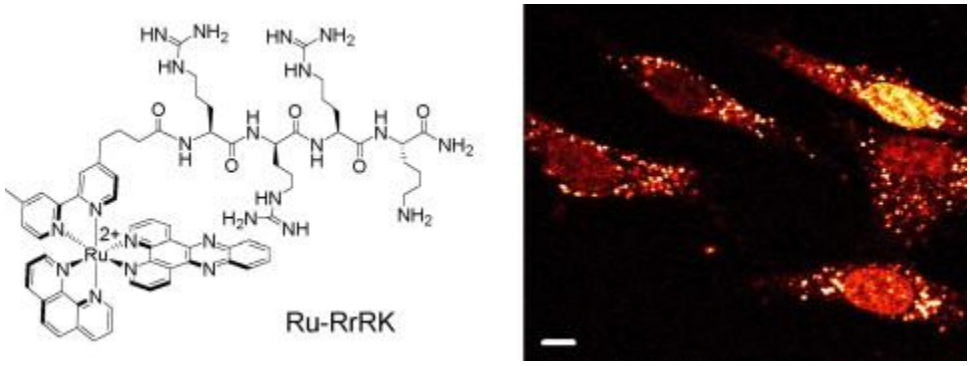
Abstract



In an effort to develop octahedral metal complexes as chemotherapeutic and diagnostic agents targeted to DNA, it is critical to optimize the properties of their cellular uptake. Appending D-octaarginine has been found to improve both the uptake and nuclear localization efficiency of these complexes, but the increased positive charge interferes with selective DNA binding and hence activity. Herein, we evaluate the nuclear entry of a series of luminescent ruthenium peptide conjugates of shorter sequence and lower charge. As is the case for the D-octaarginine conjugate (Ru-D-R8), the tetrapeptide RrRK (where r = D-arginine) facilitates nuclear localization of the ruthenium complex above a threshold concentration, though the threshold is higher for this conjugate (Ru–RrRK) than for Ru-D-R8. Furthermore, appended fluorescein, which lowers the threshold concentration for Ru-D-R8, does not improve nuclear entry of Ru–RrRK, indicating that fluorescein conjugation is not a general strategy for modulating the distribution of cellpenetrating peptides. Similarly, the concentration required for nuclear entry of Ru–RrRK is much higher than has been reported for a thiazole orange RrRK conjugate, demonstrating the influence of payload on the efficiency of uptake and localization of cell-penetrating peptides.

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