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Cytotoxic effects and intracellular trafficking pathways of conjugates of AFP receptor binding domain with different charged PAMAM dendrimers in tumor cells

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Human alpha-fetoprotein (AFP) and AFP receptor binding domain (AFPRbd) are able to bind and internalize effectively by wide range of human tumor cells and tissues. As other vector molecules AFPRbd has insufficient quantity of chemical groups which can be conjugated with drugs or diagnostic agents. Conjugation of vector molecules with macromolecular polymer carriers like dendrimers aims to solve this problem. Our study describes influence of AFPRbd-dendrimer-doxorubicin conjugate surface charge on intracellular trafficking routes and toxicity. The amine-terminated (G2) and acetyl-terminated (G212) 2nd generation PAMAM dendrimers carrying doxorubicin (Dox) were used to synthesize conjugates with AFPRbd. Unmodified by AFPRbd G2 and G212 dendrimer derivates labeled with Dox were absorbed by the cells at 37°C with different efficiency. G212-Dox derivate characterized much slower internalization rate than non-acetylated G2-Dox. Only G212-Dox shown partial colocalization with lysosomal marker LAMP2 after 4 h of incubation. Internalization of AFPRbd-G2-Dox and AFPRbd-G212-Dox did not show significant difference. At the same time, both conjugates contained AFPRbd were almost fully associated with LAMP2 already after 30 min of incubation. Cytotoxicity results revealed that IC50 levels of G212-Dox and AFPRbd-G212-Dox coincided and demonstrated a bit higher activity against sensitive to Dox SKOV3 and resistant SKVLB cells than AFPRbd-G2-Dox conjugate after 72h of incubation. At the same time, after 1 h of incubation AFPRbd-G2-Dox and AFPRbd-G212- Dox were much more than G212-Dox and G2-Dox. We may conclude that there is significant difference in ways of dendrimers internalization by tumor cells depending on nature of surface chemical groups. On the other hand, chemical modification of dendrimer conjugated with does not AFPRbd influence dramatically on the protein trafficking and resulting cytotoxic effect. Russian Scientific Foundation supported this study (№15-15-10013).

Biography

Nikita Yabbarov finished department of biochemistry of Kazan (Volga region) Federal university and have finished doctorate program of Russian Academy of Sciences in "Bioengineering" Centre. Mr. Yabbarov has experience in synthesis of conjugates and complexes of proteins and peptides (e.g. human alpha fetoprotein and epidermal growth factor) with dendrimers and evaluation of bioactivity of such conjugates and complexes *in vitro* and *in vivo*.

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