Liposomes for the active targeting of anticancer drugs against receptors overexpressed on cancer stem cells for the treatment of pancreatic adenocarcinoma

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Pancreatic adenocarcinoma (PDAC) is one of the most aggressive and devastating human malignancies with a death-to-incidence ratio of 0.99 and most of the patients presenting with metastatic disease at the time of diagnosis. More than 75% of patients who undergo surgical resection of small pancreatic tumors with clear surgical margins and no evidence of metastasis, die from metastasis within 5 years.
This strange and complicated clinical feature is related to the presence of particular type of cancer cells called cancer stem cells (CSC) (1). CSC are a small population of cancer cells, within the tumor, highly tumorigenic, resistant to conventional therapy and able to replicate cancer when transplanted in mice. Currently pancreatic CSC are believed responsible for cancer recurrence and resistance and represent a new target in PDAC therapy.
A promising approach to eradicate pancreatic CSC is active targeting. Using this strategy, drugs encapsulated in nanosystems and decorated with opportune carriers, should be delivered in a specific manner on CSC by recognition of receptors expressed on their surface. In this work, the active targeting approach was reached using liposomes decorated with hyaluronic acid (HA), containing disulfiram (DSF) and disulfiram-copper complex (DSF-CU).
This system, HA-liposomes-DSF, can represent a “bullet” to kill CSC. It is well known, indeed, that DSF and its copper complex are potent inhibitors of CSC (2) while HA is a natural ligand of CD44 receptor which is considered a surface marker of pancreatic CSC.
To prepare HA-liposomes we initially synthesized a conjugate between HA and a phospholipid (HA-DPPE) that was added during liposomes preparation. In this manner we obtained liposomes with HA functionalized surface. Liposomes were then characterized in terms of size, Z potential, drugs concentration, HA density and stability in stock and physiological conditions. To investigate the interactions between DSF and the liposomes membrane, DSC analysis were performed.
Then, the cellular uptake of fluorescent HA-liposomes on CD44 positive pancreatic cancer cell lines(PANC-1) was evaluated. We observed an increasing uptake for hyaluronated formulations in comparison to plain ones, suggesting a receptor mediated uptake.
Finally, liposomal formulation were tested*in vitro* on PANC-1 cell lines, either on parental or CSC models. Liposomal formulations showed stronger anticancer activity in comparison to the free compounds. Moreover,HA-liposomes containing DSF-Cu were tested versus plain formulation and a further decrease on cells viability was observed.

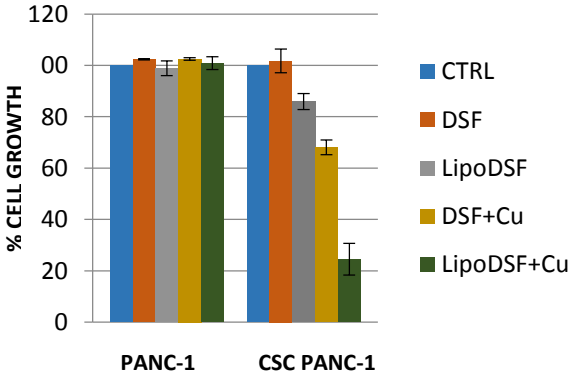

Fig 1: Cytotoxic activity of DSF and DSF-Cu liposomes on PANC-1 cells (parental and CSC) at 72 h and 100 nM.

References

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