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Workshop

Double targeting as an effective anti-cancer strategy



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A good example of an effective anti-cancer strategy can be found in nature. Cytotoxic lymphocytes (CTL) can specifically recognize the “wrong” cell than inject the granzyme B that activates caspases that cause inevitable apoptosis.

Like CTL modern anti-cancer drugs should be specific and effective. Targeting drugs to cancer cells provides specificity while the drug intracellular target provides efficacy. Binding/de-binding of the specific and effective parts should be provided too.

We tried to create anti-cancer drug that include all these features.

Human alpha-fetoprotein (AFP) serves as a nutrient delivery protein for embryo cells. Embryo cells internalize AFP loaded with nutrient by the specific AFP receptor (rAFP).

AFP has a hydrophobic pocket that can bind vital omega-3 nutrient docosahexaenoic acid (DHA) with a high affinity. A tumor is considered to be the “embryo’s evil twin”. Majority of cancer cells re-express rAFP and are able to internalize AFP. That is why AFP-rAFP delivery system is used for targeted delivery of toxins to the cancer cells. Effective toxin can be fitted into the AFP hydrophobic pocket instead of DHA. The toxin choice is important: it should bind AFP with high affinity and like granzyme B it should provide inevitable cell death. Majority of the chemotherapy do not bind AFP competitively to albumin. The toxins with high affinity to AFP should be found first. Second, inevitable cell death can be provided by the toxins that are targeted to mitochondrion, EPR, lysosome, peroxisome and their membranes or - like CTL granzyme B - to caspases. These toxins cause effective apoptosis induction instead of ineffective inhibition of proliferation that traditional drugs (targeted to DNA or tubulin) do.

Atractyloside is known embryo toxin that indicates its ability to bind AFP competitively to albumin, to cross placenta and damage embryo cells. Binding/de-binding of atractyloside to AFP is going in natural way (like AFP-DHA). Atractyloside is a powerful toxin targeted to mitochondrion. MDR of cancer cells is overcome by atractyloside and other toxins that are targeted to mitochondrion, EPR, lysosome, peroxisome and their membranes because they are points of “no return” in cell death cascades.

Oral formulation of porcine AFP complex with atractyloside (aimpila) has shown good results in mice cancer model and in mCRC cancer patients. Aimpila leads to quick metastasis reduction, improves survival of cancer patients and quality of their life.

Cancer stem cells are close to embryo cells and should have rAFP with high probability. Atractyloside unlike traditional chemotherapy can destroy not only fast but also slow growing cancer cells (including cancer stem cells). Aimpila and similar drugs have perspectives in prevention and treatment of metastasis.