Extracellular ATP is “swallowed” by cancer cells through macropinocytosis and promotes their survival and drug resistance

Despite progress made in research of the Warburg effect, the biological reasons for ATP synthesis by aerobic glycolysis in cancer cells are only partially understood. Intriguingly, intratumoral (extracellular) ATP levels are $10^3$ to $10^4$ times higher than those in normal tissues. We recently showed that although extracellular ATP is not known to cross the plasma membrane by itself, extracellular ATP in the range of the intratumoral ATP levels induced large intracellular ATP concentration increase in A549 human lung cancer cells. Based on these results, we hypothesized that extracellular ATP is taken up by cancer cells and promotes cancer cell survival. Here we report that, a nonhydrolyzable fluorescent ATP was internalized by A549 human lung cancer cells through macropinocytosis, a process known as non-specific large fluid drinking. The induced ATP increase, which involved neither transcription nor translation, was reduced by the macropinocytosis inhibitor EIPA but persisted even when mitochondrial oxidative phosphorylation and glycolysis were inhibited. The increases were also observed in several other cancer cell lines, but not in noncancerous cells. Furthermore, extracellular ATP enhanced cancer cell survival under various stress conditions and promoted drug resistance to tyrosine kinase inhibitors that compete with ATP for their anticancer action. Together, these results provide the first evidence that extracellular ATP is internalized by cancer cells via macropinocytosis, which significantly contributes to their growth and drug resistance. These findings potentially change our understanding of ATP supply and sharing among cancer cells, expanding the current interpretation of the Warburg effect and highlighting a novel anticancer target.

References:

