Metalloimmunotherapy: Combination of cisplatin and STING agonist into one molecule boosts cancer immune response

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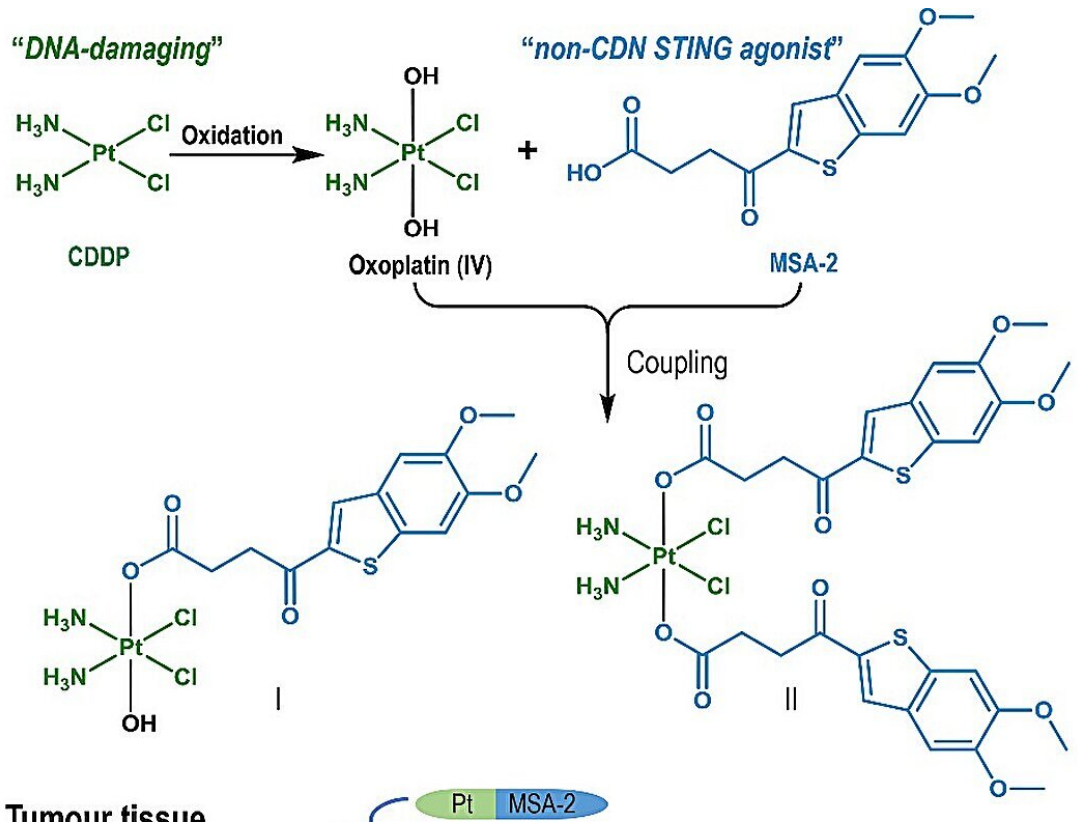

Schematic illustration of the construction of conjugates I and II. Schematic illustration of the combinational effects on tumors of the Pt^{IV}-MSA-2 conjugates. The Pt^{IV}-MSA-2 conjugates are reduced to Pt^{II} species and MSA-2 in tumor tissues. The Pt^{II} species kill tumor cells, causing the release of DNA fragments to activate STING in DCs, which is also amplified by free MSA-2. STING activation in DCs promotes IFN-β secretion to activate $CD8^+$ T and NK

cells, which release IFN-γ and GzmB for tumor killing. All these factors eventually amplify the antitumour therapeutic effects. Credit: Science China Press

Traditionally, therapies combining DNA-damaging agents and STING agonists have shown potential in treating cancer by enhancing immune response and reshaping the tumor microenvironment. However, until now, creating a single molecular entity housing both agents has remained elusive.

Enter the game-changer—two Pt-MSA-2 conjugates (I and II). These ingenious compounds bring together the DNA-damaging power of cisplatin and the immune-activating strength of STING agonist MSA-2. Excitingly, these conjugates exhibit remarkable potential as versatile small-molecule drugs specifically targeting pancreatic cancer.

Detailed studies uncovered that conjugate I not only elevated the expression of innate immunity and metabolism-related transcripts in cancer cells but also demonstrated a distinct profile compared to cisplatin and MSA-2. Exploring the tumor microenvironment revealed that conjugate I could boost the infiltration of natural killer (NK) cells into tumors and trigger the activation of T cells, NK cells, and dendritic cells (DCs) within tumor tissues.

This finding suggests that conjugate I, born from the fusion of a Pt chemotherapeutic drug and a STING agonist, stands as a promising and potent candidate for anticancer drug development. This opens up exciting new avenues for metalloimmunotherapy, marking a significant stride in the ongoing battle against cancers.

The research is published in the journal *National Science Review*.

More information: Shuren Zhang et al, Combining cisplatin and a STING agonist into one molecule for metalloimmunotherapy of cancer, *National Science Review* (2024). DOI: 10.1093/nsr/nwae020