Targeted Tumor Therapy: When Antagonists Do the Better Job

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Targeted tumor therapy lobs toxic payloads directly into tumors to destroy cancer cells while leaving normal cells unharmed. In the case of radiotherapy, these missiles, which should unerringly home in on the target and make it implode, consist of radioactive bullets guided by small molecules—known as agonists—that recognize and then activate specific receptors over-expressed on the surface of tumor cells.

But a team including researchers at the Salk Institute for Biological Studies and collaborators in Switzerland now shows that it may be better to exploit small molecules that antagonize rather than activate receptors. Those findings appear in this week's Early Online Edition of the *Proceedings of the National Academy of Sciences*.

"Our findings mark a paradigm shift," says Jean Rivier, a professor in the Clayton Foundation Laboratories for Peptide Biology at the Salk. "In the past, radiolabeled antagonists were never considered for targeted cancer therapy since they don't trigger the internalization of the receptor/ligand complex, which was thought to be the critical step towards accumulation of the payload. But we found that antagonists have other properties that may considerably improve the sensitivity of diagnostic procedures and improve the efficacy of receptor-mediated radiotherapy," he adds.

Radiotherapy, a promising tool in the arsenal against cancer, delivers lethal molecules directly to a tumor. For example, peptide hormone-producing tumors, which express receptors for another hormone,

somatostatin, are routinely targeted with radiolabeled somatostatin agonists to diagnose and treat the tumors.

A normal function of somatostatin, which was isolated in 1973 by Salk researchers, is to block release of growth hormone. However, synthetic somatostatin receptor agonists have been radiolabeled and used to treat neuroendocrine tumors. Although these strategies are quite successful, improved tumor uptake and reduced toxicity to organs like the kidney are still desirable.

Agonists have traditionally been favored in targeted therapy since they and their activated receptors readily slip inside cells taking the attached radionuclide with them, destroying them from within. Radiolabeled antagonists, on the other hand, remain marooned outside the cell and hence, have never been considered for tumor targeting.

However, the fact that in some cases radiolabeled antagonists bind to a greater number of receptors than agonists led the research team to reconsider tumor targeting properties of the long-ignored antagonists.

Rivier's lab designed and synthesized several synthetic somatostatin receptor antagonists, and then senior author Jean Claude Reubi, MD., a professor at the Institute of Pathology at the University of Berne in Switzerland and adjunct professor at Salk, selected the most effective ones based on in vitro assays.

"Amazingly, we identified, after multiple trials, errors and refinements, antagonists that had very high binding affinity, were selective for one receptor subtype only and did not trigger receptor internalization at all, thus providing the ideal tool to test the validity of the above postulate," says Reubi.

The question of whether this discovery had any practical application was

readily answered in vivo in cancer tumor-bearing mice, when co-author Helmut R. Mäcke, Ph.D., a professor at the University Hospital, Department of Radiology in Basel, Switzerland, loaded the missiles with radioactive warheads aimed at tumors expressing somatostatin receptors.

“One of the most impressive findings is that the amount of uptake of the antagonist-driven radioligands is particularly high in these tumors,” says Rivier. “As a matter of fact, a 60 percent uptake of all administered radioactivity has never been achieved before by any somatostatin receptor agonist, not even the newest ones,” he adds.

The study revealed that lethal radioactivity remained or persisted in tumors for up to 72 hours. But what pleased the scientists most was the high tumor/kidney uptake ratio. “This is the critical number for clinical use. If you want to treat patients, the radiation dose received by normal tissue, and the kidneys in particular, has to be kept at a minimum,” says Rivier.

But why are antagonists more effective than agonists, since antagonists are reduced to hanging onto the outside of cells? Rivier explains that agonists, although they internalize, bind to a limited number of receptors, making them a less efficient target than an antagonist that may be able to bind to a greater variety of receptor conformations.

"This finding has paramount consequences for the future expansion of nuclear medicine," says Reubi. Mäcke, who is highly experienced in in vivo radionuclide targeting, also acknowledges the significance of using antagonist rather than agonist guidance systems, saying, "It is by far the most significant conceptual and pragmatic development of the past ten years."

Also contributing to the work were co-first authors Mihaela Ginj, Ph.D., and Hanwen Zhang, Ph.D., Damian Wild, MD., and Xuejuan Wang,

MD., all in the Mäcke laboratory; Beatrice Waser and Renzo Cescato, Ph.D., in the Reubi laboratory; and Judit Erchegyi, Ph.D., in the Rivier laboratory.

Source: Salk Institute for Biological Studies