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Cover Story

Noninvasive imaging of MT1-MMP-positive tumors

Noninvasive molecular imaging techniques are now well-established and indispensable diagnostic tools not only in the clinic but also in the research laboratory for preclinical applications. Molecular imaging clarifies and visualizes the molecular processes of particular biological targets in living subjects and holds great potential for early detection of diseases, monitoring targeted drug delivery, and evaluation of therapeutic regimens. Specific, noninvasive imaging at the target sites, however, can only be achieved by using targeted imaging probes. In general, the utilization of binding ligands, such as peptides and proteins, can significantly improve the performance of imaging modalities [1]. For this reason, discovery of a ligand that specifically binds to molecular targets is one of the most critical steps for further advances in this field. Phage display technology is widely applied in screening novel binding ligands; however, the current ligands obtained by the phage display are limited by their low affinity and specificity to the targets. In addition to the traditional screening targets, such as proteins, intact cells or extracted organs, one promising alternative target is a peptide that is specific to a certain molecule.

Matrix metalloproteinases (MMPs) are a family of zinc dependent endopeptidases and play a crucial role in diseases such as cancer [2]. Since MMP activities are responsible for various pathological disorders, MMPs have been important therapeutic targets. Twenty-three human MMPs have been identified and can be categorized as extracellular MMPs and membrane type MMPs. Noninvasive imaging of MMP activities could provide a number of clinically valuable information including the detection of different stages of tumors with increased activity of MMPs, monitoring the efficacy of anticancer treatment, and screening drug candidates whose biological action can alter MMP expressions. To date, most MMP imaging has been focused on extracellular MMPs because of the ease of accessibility *in vivo* [3]. Although the essential roles of membrane type-1 MMPs (MT-MMPs) have been reported, no noninvasive imaging technique has been able to show clear visualization of MT-MMP expression *in vivo* due to the lack of specific imaging probes for MT-MMPs.

In an article described in this issue, Dr. Chen and his coworkers presented a successful usage of a synthetic peptide as a target for phage display peptide library panning and proved their concept by obtaining a specific membrane type-1 MMP (MT1-MMP) affinity peptide [4]. The key feature of this panning strategy is the use of a synthetic peptide from MT1-MMP as a target. The screened peptide has a unique binding sequence for specific regions of MT1-MMP and shows a fairly high affinity for MT1-MMP (apparent $K_d = 47.41$ nM). After the systematic validation of the obtained peptide ligand *in vitro*, they were able to noninvasively image MT1-MMP expression in MT1-MMP-positive tumor models, for the first time, by using a near-infrared dye-labeled MT1-MMP affinity peptide. The technique described by Dr. Chen and his colleagues presents a highly effective approach on conventional methods to search for affinity peptides onto other types of transmembrane proteins. Screened lead peptides can be used as ligands for imaging probes or drug delivery carriers targeting other types of transmembrane proteins *in vivo*.

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