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Cathepsin nanofibers substrates for targeted drug delivery

The development of reactive drug carriers that could actively respond to biological signals is a challenging task. Different peptides can self-assemble into biocompatible nanostructures of various functionalities, including drug carriers. Minimal building blocks, such as diphenylalanine, readily form ordered nanostructures. Here, we present development of self-assembled tetra-peptides that include the diphenylalanine motif, serving as substrates of the cathepsin proteases. This is of great clinical importance as cathepsins, whose activity and expression are highly elevated in cancer and other pathologies, have been shown to serve as efficient enzymes for therapeutic release. Based on the cathepsins affinity around the active site, we generated a library of Phe-Phe-Lys-Phe (FFKF) Tetra-Peptide Substrates (TPSs). We inserted various N-termini capping groups with different chemical properties to investigate the effect on protease affinity and self-assembly. All 9 TPSs were cleaved by their targets, cathepsins B and L. However, solvent switching led to nanofibers self-assembly of only 7 of them. Due to its rapid self-assembly and complete degradation by cathepsin B, we focused on TPS4, Cbz-FFKF-OH. Degradation of TPS4 nanofibers by cathepsin B led to the release of 91.8±0.3% of the incorporated anti-cancerous drug doxorubicin from the nanofibers within eight hours while only 55±0.2% was released without enzyme treatment. Finally, we demonstrated that tumor lysates fully degraded TPS4 nanofibers. Collectively, these results suggest that tetra-peptide substrates that form nanostructures could serve as a promising platform for targeted drug delivery to pathologies in which protease activity is highly elevated.

Biography

Galia Blum has her main research focus on the generation of novel chemical probes targeted to proteolytic enzymes and their application for medical uses such as molecular imaging and therapy. She also applies her original probes for basic research investigating the involvement of proteases in normal and pathological conditions. Over the years at the Hebrew University her group among other projects has developed novel probes for caspase-3 and discovered its activity in the ER and developed novel photodynamic probes targeted to cathepsin proteases and used them for combined detection and therapy of cancer. Recently, she also began working on the nano-scale materials where she developed novel protease sensitive drug delivery molecules (Ben-Nun 2016) and nano-probes for CT molecular imaging.

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