Universidade de São Paulo
Instituto de Física de São Carlos

Semana Integrada do Instituto de Física de São Carlos

13ª edição

Livro de Resumos

São Carlos
2023

Ficha catalográfica elaborada pelo Serviço de Informação do IFSC

Semana Integrada do Instituto de Física de São Carlos
(13: 21-25 ago.: 2023: São Carlos, SP.)
Livro de resumos da XIII Semana Integrada do Instituto de Física de São Carlos – Universidade de São Paulo / Organizado por Adonai Hilário da Silva [et al.]. São Carlos: IFSC, 2023.
358p.

Texto em português.
1.Física. I. Silva, Adonai Hilário da, org. II. Título.

ISSN: 2965-7679

PG23

Noninvasive tumor diagnostics using proteolytic activity nanosensors

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Cancer diagnosis relies fairly on clinical symptoms, imaging, detection of endogenous biomarkers in blood circulation, and invasive biopsies. (1) However, cancer progresses in silence featuring confusing symptoms, lesions below the level of imaging detection, low concentration levels of clinically relevant biomarkers in biofluids, and often limited tissue for sampling, curtailing the benefits of early tumor detection. (2) To tackle it, an emerging diagnostic strategy is deploying responsive nanodevices as pro-diagnostic agents to sense molecular changes in the tumor microenvironment and generate an amplified readout in biofluids. Tailored-assembled biosensors respond to matrix metalloproteinase upregulated catalytic activity in tumor invasive regions by shedding upon activation a synthetic urinary biomarker that concentrates into the urine. (3) We synthesized nanosensors by reacting an aminated inert carrier of [8-arm-poly(ethylene oxide)]40kDa, sulfhydryl-reactive-handle-terminated crosslinker (53,4 Å) of a pegylated spacer, and cysteine-terminated substrates of matrix metalloproteinase-2, containing the substrate and the synthetic biomarker linked by a peptide bond. The nanosensor molecular assembly was confirmed by its optical properties. Toxicity studies of blood markers showed that the sensor does no harm when traveling through the bloodstream. As representative formulations of our nanosensor, fluorescent probes were synthesized and successfully activated in vitro by a protease that plays a role in tumor angiogenesis. The nanosensor and synthetic biomarker half-lives in plasma and urine revealed the potential use of our nanosensor as a pro-diagnostic agent. We are putting forward a disease diagnostic validated by a mathematical framework that details relevant aspects of our nanosensor and synthetic biomarker kinetics within the body, aiming at an informed design basis of noninvasive tumor diagnostics based on activity probes.

Palavras-chave: Nanomedicine. Biosensors. Synthetic biomarkers.

Agência de fomento: CAPES (88887.474259/2020-0)

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