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Noninvasive tumor detection using activity nanosensors

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Challenges in early tumor detection persist regardless all the advances in cancer care. Lung cancer has been consistently diagnosed at later stages along with ovarian and rapid-growing breast cancers, curtailing the health system treatment options. (1-2) All because there is no diagnostic technology amenable to screen the general and the high-risk populations. (2) One way to push boundaries in noninvasive early cancer detection is by developing engineered synthetic biomarkers coupled with nanoparticles capable of sensing proteolytic activity in tumor microenvironment and shedding inert peptides that undergo glomerular filtration, enabling them to concentrate into the urine and serving as tumor biomarkers. (3) Hereupon, nanosensors act as pro-diagnostic agents leveraging in dysregulated catalytic activity of solid tumor proteases and urinary enrichment to create and amplify signals from diseased sites that otherwise would be undetectable.(1,3) We identified overexpressed proteases in human ovarian and breast cancers by performing differential analysis on data from gene expression omnibus using DESeq2 R package. We assembled our nanosensors in a two-step reaction via N-hydroxysuccinimide and maleimide chemistries to direct query tumors for MMP-2 activity in breast and ovarian cancer models in mice, which tolerate the nanosensors without triggering adverse systemic response or toxicity measured by the levels of biomarkers of hepatoxicity in blood and sensor cytotoxicity on target organ cells. We demonstrated that MMP-2 is activated in vitro by monitoring fluorescence resonance energy transfer substrate cleavage and its activation follows the Michaelis-Menten model, which allowed the estimation of synthetic biomarker cleavage kinetic parameters. Since the clinical relevance of the enhanced permeability and retention effect is disputable, we tackle this underlying issue in our approach by generating a pharmacokinetic model to track our nanosensors into solid tumors and framework our understanding on how physiological parameters would affect our interpretation of the synthetic biomarker concentration in urine as a signal of tumor presence. Our model is a system of ordinary differential equations derived from the macroscopic mass balances of nanosensor and synthetic biomarker in blood, tumor and bladder, and the Fick's law to account for the nanosensor diffusional-control transfer from blood to tumor. Experimental data were collected by deploying and combining fluorimetry and SDS-PAGE electrophoresis. Parameter estimation was performed in MATLAB using the built-in function ODE15s and the simulations using ODE45 with adaptive Dormand-Prince method in SIMULINK. Amplification of synthetic biomarker signal reaches 150 times concentration in urine and the half-life of nanosensor shows that the nanosensor residence time in blood is suitable for probing active tumors. Immunochromatographic tests detect the circulating synthetic biomarker in 30 min at nanogram levels. We are looking to detecting noninvasive and early disease signals by overcoming the mass transport limitations of pity amounts of endogenous tumor biomarkers along with short residence times and random degradation in blood via the catalytic nature of synthetic biomarker generating in tumor microenvironment and urine enrichment, opening a window of opportunity to detect tumors when they are curable.

Palavras-chave: Nanomedicine; Biosensors; Synthetic biomarkers.

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