Fetuin-a-based theranostics in ectopic calcification

SUMMARY

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Calcium is an essential component of the human body that accounts for approximately 2% of body weight. Due to its direct involvement in a multitude of physiological processes, its metabolism is precisely regulated. Biomineralization is the process by which calcium is incorporated into body tissues to harden them in order to ensure their physiological functions. In humans, biomineralization is restricted to bones and teeth and is actively prevented in other tissues by a network of circulating and local inhibitors of calcification. Endocrine disorders, inflammatory and age-related diseases can interfere with this network, resulting in buildup of calcium phosphate deposits in soft tissues in a process known as ectopic calcification. Such abnormal deposition of calcium salts can stiffen the blood vessels or worsens the course of atherosclerosis, leading to severe and even lethal complications such as myocardial infarction or stroke. While it is possible to visualize large calcified lesions, pro-inflammatory micrometer-sized calcium deposits are hard to detect using conventional imaging techniques. Regardless of the size of the calcifications, there are currently no conservative treatments to eliminate existing calcium salt deposits. The aim of current work was to develop approaches to imaging and treatment of ectopic calcifications using.

Fetuin-A is a liver-derived circulating inhibitor of calcification that acts by preventing the precipitation of calcium phosphate. Its high affinity to calcium-rich minerals is explained by its unique structural properties as well as by its molecular charge distribution. A set of fluorescent calcification probes was generated by attaching fluorescent proteins to a molecule of murine fetuin-A. The novel probes were proven to be non-toxic and suitable for imaging calcification on living cells, surpassing the traditional staining techniques. Moreover, the fetuin-A-based probes were shown to be much sensitive toward microcalcifications than the chemical dyes, which were often leaving the smallest calcified lesions unstained. Finally, the novel probes labeled with a radionuclide were used for intravital imaging.

Bone resorption by osteoclasts is the only natural process in which otherwise insoluble calcium salt is being broken down. Differentiation and activation of bone-resorbing osteoclast essentially depends on a cytokine called RANKL. By fusing RANKL with fetuin-A, I obtained an effective tool for targeted activation of osteoclasts at calcification sites. Collectively, fetuin-A-based fusion proteins show a promising theranostic potential for ectopic calcification.