The Applications of Ultrasound Microbubbles in Molecular Diagnosis and Therapy

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Ultrasound imaging is one of the most common diagnostic modalities used in clinics because of superior safety, low cost and easy accessibility compared with other conventional imaging modalities like magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography (PET) (1,2). The application of ultrasound imaging ranges from first-look examinations of soft tissues such as abdomen or female genital tract and intravascular applications (1).

Recently, much attention has focused on observation of microcirculation in different kinds of abnormalities or diseases in tissues such as the dependence of angiogenesis on tumor growth and the importance of noninvasive visualization of tumor microvasculature to determine treatment strategies (3). However, the specificity and sensitivity of ultrasound imaging are susceptible to low contrast differences between tissue and blood. Conventional Doppler imaging only permits flow assessment of vessels larger than hundreds of micrometers, like arterioles.

These limitations have been overcome by gas-filled microbubbles as intravascular ultrasound contrast agents (UCAs) (2). Microbubbles are routinely used to assess microcirculation in tumors and soft tissues, myocardial perfusion, heart function and also to assess therapy response (1).

Gas-filled microbubbles for ultrasound contrast enhanced imaging usually have a diameter between 1 and 4 mm, thus restricting them to the vascular system. Microbubbles have made from free gas bubbles in solution stabilized by surfactants to bubbles with a shell made from phospholipids, polymers or proteins (1).

Cell and tissue specificity can be achieved by using passively or actively targeted microbubbles. Passive targeting refers to the use of intrinsic properties of microbubble shell. Active targeting refers to the use of noncovalent or covalent attachment of specific targeting moieties to the microbubble shell, to permit for binding to specific receptors (4).

Molecular imaging can be realized by binding targeting moieties to microbubble surfaces. Molecular microbubbles directed against various targets such as vascular endothelial growth factor receptor-2, and integrins were shown in preclinical researches to be able to selectively bind to tumor blood vessels and atherosclerotic plaques (5).

Gas-filled microbubbles can be used for: thrombolysis, gene and drug delivery across biologic barriers. High-frequency ultrasound can be used in order to dissolve thrombi. This effect is mostly the result of stable and/or inertial microbubble oscillation and cavitation, leading to clot destruction (6). Besides thrombolysis, the application of ultrasound plus microbubbles holds valuable potential for improving gene and drug delivery across biologic barriers. In this field, focused ultrasound refers to the concentration of acoustic energy on a focal spot a few millimeters in diameter. Depending on the energy used, biologic effects like heat-induced coagulation can result. However, acoustic pressures induced by microbubble destruction with low ultrasound energies can also temporarily increase cell membrane permeability and/or blood vessel in the insonated region, thereby enhancing local gene and/or drug delivery (1).

Gas-filled microbubbles were designed as ultrasound contrast agents (UCAs) to improve the sensitivity of conventional ultrasound imaging.

The uniqueness of microbubbles, including bioconjugation, drug encapsulation, cavitation, and nonlinear emission, permit them to be used simultaneously as diagnostic and therapeutic agents. Taking the diagnostic and therapeutic potential of microbubbles, we can conclude that ultrasound imaging in combination with microbubbles provides a valuable and versatile tool for molecular imaging and therapy.

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