Selective synovectomy using thrombin-sensitive photodynamic agents

Rheumatoid arthritis is an autoinflammatory disorder, a systemic disease in which the body’s own defense system reacts in an unregulated manner to cause overgrowth of the synovium. Synovium is a thin layer of cells that lines and lubricates the joints. As a consequence the synovium becomes engorged with new blood vessels and infiltrated with inflammatory cells, thus further damaging the cartilage and the bone. In the 19th century, when the disease was given its name, those who suffered from rheumatoid arthritis, including master Impressionist Pierre-Auguste Renoir, found it very difficult to conduct their ordinary daily activities. Patients in modern days, however, have been benefiting from the advances in medicinal chemistry. It is estimated that about 70% of all rheumatoid arthritis patients can be easily treated with various medications that can relieve pain by reducing inflammation in the joints. Although rheumatoid arthritis cannot be cured, joint damage can be slowed or prevented by early treatments using an armada of drugs, such as pain killers, anti-inflammatory drugs, corticosteroids and different cytokine inhibitors. The remaining 30% of the patients, however, suffer from persistent, chronic synovitis, and may require much more invasive treatment options, such as surgical, chemical, and radioisotopic synovectomy. Ideally, the latter should be replaced by less invasive approaches. One of such approaches is photodynamic therapy (PDT). In PDT a patient is administered with a photosensitizing agent that accumulates in the diseased tissue. Upon activation by light, the photosensitizer catalyzes the conversion of molecular oxygen into highly reactive oxygen species, which in turn, destroy the target tissue. In principle, PDT is an ideal therapeutic strategy for the treatment of rheumatoid arthritis, since the success of the treatment critically depends on the concomitant presence of all three components involved in this treatment modality. Thus, the PDT does not affect those parts of the joint that are not oxidized, such as the cartilage, and those parts where light penetration is minimal, such as the bone, bone marrow, or non-irradiated sites of the body.

Despite the potential advantages, PDT has not been translated into clinical practice. This is in part due to the commonly reported drawbacks of conventional photosensitizers which have limited selectivity, low hydrophilicity, poor pharmacokinetics, and weak absorption in spectral regions where tissue penetration of light is optimal. The article by Nobert Lange and his colleagues in this issue [1] reports the development of a new photosensitizer that seems to resolve most of the issues faced with conventional photosensitizers. The new photosensitizer developed in the article is based on the combination of the polymeric prodrug approach [2] and quenched probes [3]. Nobert Lange exploited the up-regulation of thrombin activity in rheumatoid arthritic joints, and constructed a polymeric prodrug that is sensitive to endoprotease. Photosensitizer units were attached to a polymeric carrier via a peptide linker that can be cleaved by thrombin. In the study, as much as 30 photosensitizer units were tethered to one polymer chain. The photosensitizers in the polymeric form do not fluoresce due to self-quenching, and as a result, they cannot generate reactive oxygen species. In the presence of thrombin, however, the photosensitizer units are released from their polymeric carrier, thus restoring photoactivity. In their paper, Nobert Lange and his group show that cell killing can only be achieved in the presence of thrombin. Furthermore, selective activation of the thrombin-cleavable polymeric delivery system was shown in an in vivo animal model for rheumatoid arthritis on a single joint level. The molecular imaging study with the polymeric delivery system showed that the fluorescence intensity correlated well with the clinical score attributed to the respective joints. Interestingly, as shown on the cover figure, the activated and non-activated constructs not only differ in fluorescence intensity but also in their emission spectrum, allowing clear distinction between both states in vivo through spectral unmixing.

The findings by Nobert Lange and his team clearly provide new possibilities of selective PDT of rheumatoid arthritis in the near future. The prodrug approach used by the team can easily be extended to a host of other photosensitizers. Since the photosensitizers become fluorescent only after activated by thrombin-induced cleavage, they are ideal for therapy and diagnosis (theranosis or theragnosis). Since peptide linkages can be constructed for degradation only by a specific enzyme, this prodrug approach can be used to develop other constructs for selective delivery of other anti-arthritic drugs based on specific target enzymes. The prodrug approach is one of the widely used approaches in drug delivery, and its usefulness has been well documented. Combining the prodrug approach with molecular imaging has generated a new, highly powerful approach for selective drug delivery that can be useful not only for photosensitizing agents but also for various drugs in general.

References


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