Bioreductive fluorescent probes to image different levels of hypoxia in human and plants.

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ABSTRACT

Hypoxia (low oxygen levels) occurs in a range of biological contexts, including plants (development and waterlogging),[1] bacterial biofilms, and solid tumors.[2] It elicits responses from these biological systems that impact their survival, for example, hypoxia makes tumors more resistant to all forms of therapy and leads to poor patient prognosis.[2] Hypoxia in the tumor microenvironment is heterogeneous (with O_2 ranging from 0-6%) and its effects differ in an oxygen-dependent manner.[3] Therefore, chemical imaging probes that enable the study of biological hypoxia are valuable tools to increase our understanding of disease- or development-related conditions that involve low oxygen levels. Most existing small-molecule hypoxia-sensing images only very severe hypoxia ($\leq$1% O_2).[4] Furthermore, commonly used antibody-based imaging tools for hypoxia are less convenient, as a secondary detection step involving immunostaining is required. Therefore, we have developed an efficient synthetic methodology that affords a palette of bioreductive fluorescent probes which are activated at a range of oxygen levels (0-6%) with emission maxima ranging through red, orange, and green. The deployment of these probes in human cell cultures,[5] and for the first time in both plant cells and tissues (including endogenously hypoxic roots),[6] enables the imaging of different levels of hypoxia with unprecedented details, providing convenient alternatives to antibody-based imaging approaches. These probes have the potential to facilitate a greater understanding of oxygen dynamics in plants, allowing the correlation of oxygen concentrations with adaptive and developmental responses to hypoxia.

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