Hypoxia truncates and constitutively activates the key cholesterol synthesis enzyme squalene monooxygenase

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Cholesterol is a vital component of cell membranes, yet its synthesis is highly oxygen- and energy-intensive. Accordingly, cholesterol production is tightly regulated by metabolic feedback and feedforward loops. A nexus for this regulation is the first oxygen-dependent enzyme of the pathway, squalene monooxygenase (SM, or SQLE), which undergoes ubiquitin-dependent degradation under cholesterol-rich conditions. Here, we sought to identify other regulators of SQLE degradation—and therefore flux through cholesterol synthesis—by testing the effect of oxygen restriction on its stability. We found that hypoxia induces the rare phenomenon of partial proteasomal degradation, converting SQLE to a truncated yet catalytically active variant that is long-lived and resistant to cholesterol-induced degradation. Importantly, this response is sensitive to a range of oxygen tensions and observed in patient-derived endometrial tumours. SQLE truncation requires the E3 ubiquitin ligase MARCHF6 and is directly stimulated by its substrate squalene, which accumulates during hypoxia and interferes with the processivity of SQLE degradation. Ultimately, proteolytic activation of SQLE compensates for reduced availability of its cofactor oxygen to preserve catalytic activity. During temporary oxygen shortfalls this allows continued cholesterol synthesis, while at longer timescales it ensures downstream accumulation of metabolites that suppress other components of the pathway to conserve oxygen. This work is currently being related to research in James Nathan's laboratory (University of Cambridge) uncovering the hypoxia-induced and MARCHF6-mediated degradation of SREBP-2, the master transcriptional regulator of cholesterogenic genes. Together, they point towards regulatory networks that suppress oxygen-intensive cholesterol synthesis during hypoxia.