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PYROPTOSIS AS AN IMPORTANT TARGET FOR DRUG DISCOVERY

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Gasdermin family proteins mediate the proinflammatory programmed cell death pathway known as pyroptosis, which is now considered a key pathogenetic mechanism in various diseases, and targeting it opens new avenues for their treatment. For example, pyroptosis is a primary cause of inflammatory diseases. Unlike apoptosis, it is characterized by the formation of holes in the cell membrane, cellular swelling, and intense release of the proinflammatory cytokines IL-1β and IL-18. Two fundamentally different approaches used in the therapeutic paradigm are the activation of pyroptotic cell death as a new strategy for cancer immunotherapy and the prevention of pathological pyroptosis in autoimmune and chronic inflammatory diseases. One of the most studied targets in the regulation of pyroptosis is the NACHT domain of the NLRP3 protein. It is a central "switch" that ensures the assembly of the NLRP3 receptor into an active inflammasome complex. It is essential for initiating innate immunity and producing proinflammatory cytokines. Critical inhibitor binding sites in the NACHT domain of NLRP3 were identified through structural studies, and the compound MCC950 demonstrated potent inhibition by stabilizing the inactive conformation through interaction with residues of the Walker A motif. Natural compounds such as cryptotanshinone and salidroside downregulate the NLRP3/caspase-1/GSDMD axis in inflammatory and cardiovascular diseases by activating the Keap1-Nrf2 pathway and reducing oxidative stress. By directly binding to Keap1 at Arg415, cryptotanshinone inhibits vascular smooth muscle cell pyroptosis in abdominal aortic aneurysms, enhancing the nuclear translocation of Nrf2 and subsequent activation of cytoprotective genes such as Hmox-1. By inhibiting the JAK-STAT pathway, ruxolitinib reduces macrophage pyroptosis in aplastic anemia, while catalpol protects against diabetic cardiomyopathy by activating AMPK/SIRT1. Conversely, combined CDK and MEK inhibition enhances $CD8^+$ T-cell-mediated antitumor immunity and induces pyroptosis in head and neck squamous cell carcinoma by activating the caspase-8/GSDME pathway. This synergistic combination induces potent immunogenic cell death by increasing ROS generation, caspase-8 cleavage, and GSDME-N formation. VDAC1 is another important target for pyroptosis regulation. For example, the balasubramide derivative (+)-3C-20 binds to VDAC1 at residues Y022 and K028, preventing oligomerization and release of mtDNA, exhibiting lung tissue-specific anti-inflammatory activity in acute lung injury. The pharmacokinetic limitations of drugs that target pyroptosis are being overcome through the development of novel drug delivery methods, thanks to the convergence of structural, biochemical, and translational research. For example, prolonged transdermal delivery of quercetin liposomes in rheumatoid arthritis was made possible by GelMA-SilMA dual-crosslinked hydrogel microneedles with biomimetic structures that simultaneously target RIPK3-mediated necroptosis and effectively inhibit the caspase-8/caspase-3/GSDME pathway in fibroblast-like synoviocytes. Achieving target specificity to prevent extra-tissue effects, optimizing pharmacokinetic profiles for selective delivery, and developing reliable biomarkers of therapeutic efficacy, such as IL-18 blood levels and GSDMD cleavage products, remain significant challenges.

By offering precise methods to either limit pathological inflammation by inhibiting NLRP3 and modulating upstream signaling pathways or to induce potent antitumor immunity through caspase-8/GSDME activation and targeting VDAC1, the emerging paradigm of bidirectional modulation of pyroptosis represents a revolutionary therapeutic frontier. This dual strategy positions pyroptosis as a potentially important therapeutic target in a wide range of human diseases.