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EDITORIAL

Is eryptosis druggable?

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Regulated cell death (RCD) modalities such as necroptosis, pyroptosis, ferroptosis, or cuproptosis have been extensively studied as a target for cancer therapy due to their ability to ensure cell death in apoptosis-resistant tumors or to modulate tumor microenvironment through emitting multiple immunogenic signals by dying cells [1, 2]. Recent progress in the field of RCD has contributed to unraveling the landscape of cell death processes in particular cell types. For instance, there is accumulating evidence that erythrocytes display a limited set of RCD pathways undergoing senescence, eryptosis, and necroptosis [3–6]. A recent review has demonstrated that eryptosis of mature erythrocytes differs from apoptosis of nucleated cells at the level of crucial signaling pathways [7]. This is a prerequisite condition for developing eryptosis-specific pharmaceutical modulators. Overall, eryptosis is a controlled RCD of mature erythrocytes associated with cell shrinkage, membrane blebbing and phospholipid scrambling mediated primarily by intracellular Ca^{2+} elevation, reactive oxygen species (ROS) and ceramide accumulation [3, 6]. Clinically, accelerated eryptosis may result in anemia. Eryptosis-associated anemia has been reported in elderly individuals, acute cardiac failure, end stage renal disease, hypertension, metabolic syndrome, diabetes mellitus type 2, systemic lupus erythematosus, arteritis, lung cancer, etc. Thus, therapeutic interventions aiming to reduce eryptosis might be beneficial.

Which signaling pathway in eryptosis is druggable? Notably, phosphatidylserine (PS) externalization is a crucial event that defines eryptosis. Despite the importance of intracellular Ca^{2+} elevation, oxidative stress, or ceramide signaling, occasional activation of eryptosis-regulating kinases (p38 MAPK, casein kinase 1α, protein kinase C, etc.), caspase-3 and calpain, these events are not essential for eryptosis to occur [6, 7]. At the same time, phospholipid scrambling is observed in senescent or stressed erythrocytes [5]. Moreover, although PS translocation has not yet been shown in necroptosis of erythrocytes, it is evident that it is observed in necroptosis of nucleated cells [8]. Thus, it seems logical that pharmaceutical reduction of PS externalization prevents clearance of not only eryptotic, but also senescent, compromised and probably necroptotic erythrocytes that display PS on their surface. Thus, it can be assumed that our current understanding of eryptosis signaling makes it challenging to selectively inhibit this pathway without affecting other PS-exposing red blood cells. On the other hand, eryptosis induction has been suggested as a strategy for treating malaria [9]. The effectiveness of this approach is still debatable due to the complex and often conflicting role of eryptosis in malaria pathogenesis. Moreover, multiple generally accepted eryptosis-inducing agents have failed to trigger eryptosis in *P.falciparum*-infected erythrocytes [9].

Thus, although therapeutic interventions modulating eryptosis (both inhibition and induction) seem to be promising in multiple diseases, our knowledge of eryptotic machinery and signaling is limited to fully exploit options of eryptosis targeting.

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Declarations

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