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Role of cofilin in the programmed cell death induced by oxidative stress in human lymphocytes

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The balance between T-cell activation or inactivation is important for physiological immune responses and is regulated among others through the microenvironment. T-cell hyporesponsiveness can be harmful in cancer settings, but auxiliary in controlling autoimmune diseases like arthritis. Oxidative stress leads to T-cell hyporesponsiveness or T-cell death. The actin-binding protein cofilin is oxidized during oxidative stress, which provokes rapidly a stiffening of the actin cytoskeleton and T-cell hyporesponsiveness. In this work, it was shown that long-term (26h) oxidative stress leads to translocation of cofilin into the mitochondria followed by caspase-independent necrotic-like programmed cell death (PCD) in human T-cells. Notably, cofilin mutants that functionally mimic oxidation by a single mutation at oxidation-sensitive cysteins (Cys39 or Cys80) predominately localize within the mitochondria. The expression of these mutants alone ultimately leads to necrotic-like PCD in T-cells. Moreover, it was shown that oxidative stress might initiate further death pathways simultaneously in T-cells in addition to its PCD inducing effect via cofilin. Long-term oxidative stress triggers the activation of caspases, variations in the actin dynamics, and it was shown that inhibiting PARP, a nuclear enzyme better known for its cell protective effect but newly shown to mediate PCD under oxidative stress, reduces the cell death rate in T-cells. Nevertheless, these several other possible death pathways may be accessory. Thus, the oxidation and mitochondrial localization of cofilin was introduced as a checkpoint for necrotic-like PCD upon oxidative stress, that may have an implication in the understanding of the microenvironment's influence (e.g. tumor environment) on the activation of T-cells.