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Editorial
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Neuronal Cell Death or Survival in Hypoxia

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Editorial

Hypoxia, which is defined as shortage in an organ's oxygen supply, is a putatively lethal stressor for cells with high energy demands such as neurons and glial cells comprising the neural tissue. Over the years there has been rigorous and extensive research in respect to which cell death pathways are activated during a hypoxic insult. Three major cell death types are recognized, based on the distinct morphological features of each: apoptotic death, necrotic death and autophagy mediated death. Apoptotic death exhibits nuclear condensation, DNA fragmentation, cytoplasm shrinkage and at the final stages the cell dissolves into apoptotic bodies. Autophagic cell death, which can be characterized as "autophagy gone awry", presents extensive vacuolization of the cytoplasm due to increased presence of autophagosomes leading to cellular degradation. Necrotic cell death, once thought to be a chaotic procedure, nowadays is recognized as an organized cellular fate that presents itself with the presence of dead cells lacking the hallmarks of the above two types of death [1]. While the end result of each death process might be morphologically distinct, there are common molecular underpinnings and cross talk between them [2]. Futhermore, the current knowledge proposes that it should be taken into consideration that the same cell death "phenotype" might be a result of different cell death subroutines at play such as mitochondrial permeability transition driven necrosis (MPT-driven necrosis), ferroptosis, parthanatos and lysosome-depended cell death [3].

Many diverse models are employed to study hypoxia *in vivo* and *in vitro*. In vivo studies using "stroke-like" models report that at the infarct site there is formation of a necrotic center surrounded by an apoptotic penumbra, although there are also reports of penumbral autophagic cell death [4-7]. *In vivo* models reveal more about the mechanics of neuron death under hypoxic conditions. Hypoxia imposes an increased need for correct protein folding, mobilizing the cell's unfolded protein response mechanism and activating autophagy [8]. Hypoxia can also cause neurons to release abnormal quantities of the excitatory neurotransmitter glutamate affecting nearby neurons. Excess extracellular glutamate concentrations can overactivate glutamate receptors, causing an increase in cytoplasmic calcium concentration [9]. As glutamate concentration increases, oxidative toxicity can arise by the interference of glutamate with glial glutathione production and hence lowering neuronal antioxidant potential making them more vulnerable to reactive oxygen and nitrogen species [10,11]. Reduction in neuron's glutathione content has also been associated with ferroptosis, a death subroutine depending on iron ion availability, that gives a necrotic phenotype [12-14]. The aforementioned increase in cytoplasmic calcium concentration, alongside with reactive species can lead the cell to another type of necrosis called Mitochondrial Transition Pore driven necrosis, where mitochondrial pore failure is the main mediator of the forthcoming demise [15,16]. Furthermore, reactive species can initiate parthanatos in neurons, a caspase independent apoptotic like death characterised by overactivation of poly (ADP-ribose) polymerase 1 (PARP1) and subsequent nuclear DNA fragmentation [17,18].

On a molecular "executor" level, three classic classes of proteases are implicated in the final death decision: caspases, known for their role in apoptosis, calpains, calcium depended proteases, and lysosomal cathepsins. While caspases are key players in apoptosis, they can modulate autophagic response by cleaving autophagy mediators either halting or priming the cell for it [19,20]. On its turn autophagy can inhibit apoptosis [21]. Caspases and calpains have also an intimate relationship in which they can activate each other, but also calpains are capable of deactivating caspases [22]. Calpains have also been reported to cause lysosomal rupture, releasing cathepsins to the cytosol leading to necrosis [23]. Finally, the released cathepsins can effect caspases, cleaving them and activating them [24].

Drawing from the above information, one can conclude that neuronal cell death or survival in hypoxia should be addressed in the context of the accumulated knowledge with respect to cell death pathways and to the extent of their mobilization and the conditions of each experimental approach employed researching neuronal hypoxia.

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