THE IDENTIFICATION OF MOLECULAR MECHANISMS PROMOTING MACROPHAGE SURVIVAL TO PEROXYNITRITE: A FIRST STEP FOR THE DEVELOPMENT OF NOVEL ANTI-INFLAMMATORY THERAPIES

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Macrophages cope with a variety of toxic molecules in different extracellular environments, even under unfavourable conditions as at the inflammatory sites. Hence, understanding the regulation of macrophage survival may provide the bases to develop pharmacological tools leading to selective macrophage deletion, as a strategy to reduce deleterious outcomes for the host.

Our work has thus far provided important information in this direction, using peroxynitrite as a trigger for toxicity, with the identification of at least three major survival pathways promoted by molecules largely available in the inflammatory sites. Macrophages use arachidonic acid (AA) and products of the 5-lipoxygenase (5-LO) (5-hydroxyeicosatetraenoic acid, 5-HETE) or cyclooxygenase (e.g. PGE_2) pathways to promote a signalling leading to prevention of mitochondrial permeability transition (MPT)-dependent toxicity. We detected significant levels of Bad in the mitochondria of macrophages and found that the above signalling pathways converge in Bad phosphorylation, and thus in its cytosolic accumulation. Phosphorylation inhibits binding of Bad to Bcl-2, or $BclX_{L,}$ and promotes its translocation to the cytosol thus enabling Bcl-2 and $BclX_L$ to exert their anti-MPT functions. Upstream inhibition of the survival signalling promotes the mitochondrial accumulation of Bad and the rapid onset of MPT-dependent toxicity taking place soon after the mitochondrial translocation of Bax. In short, the survival strategy adopted by macrophages is simple, yet very effective: while committed to MPT-dependent toxicity by peroxynitrite, macrophages nevertheless survive by promoting Bad phosphorylation via different pathways triggered by molecules they produce and/or largely available in the extracellular milieu. This response is extremely efficient in that survival is always achieved, regardless of the damage accumulated, in the presence of nanomolar levels of AA, 5-HETE or PGE_2.