Role of poly(ADP-ribosyl)ation in oxidative stress-induced cell death and inflammatory signaling

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Poly(ADP-ribose) polymerase (PARP) enzymes cleave NAD^+ substrate into nicotinamide and ADP-ribose and attach the latter covalently to target proteins. Some enzymes of the 17 member PARP family can also polymerize ADP-ribose units onto protein targets resulting in their poly(ADP-ribosyl)ation (PARylation). Mono and poly(ADP-ribosyl)ation is involved in the regulation of various cellular processes including DNA repair, DNA replication, gene transcription and metabolism. In excessive DNA damage scenarios PARP1 activation can also cause cell death which is now recognized as a novel cell death entity called parthanatos. PARylation is a drug target in BRCA1/2 mutant cancers and preclinical data also suggest that PARP inhibition may provide therepeutic benefit in severe tissue injuries (e.g. in stroke and ischemia-reperfusion injury of the heart or intestines) and in various forms of inflammation. The underlying mechanism of the latter likely involves direct interaction of PARP1 with NFκB and AP-1 transcription factors.

Since macrophages (MΦ) are resistant to oxidative stress we set out to investigate the mechanism by which inflammatory (M1) MΦs protect themselves from oxidative stress. We found that selfprotection involves downregulation of PARP1 gene expression, upregulation of the expression of antioxidant enzymes and reprogramming cell metabolism. We are also investigating the mechanism by which PARylation regulates phenotypic changes of MΦs (e.g. shifts to M2 phenotype) that lead to the cancer promoting effects of MΦs. Moreover, we are developing several high-throughput screening (HTS) and High-Content Screening (HCS) applications to study cell fates in various cell biology models (e.g. cell death, antibody-dependent cell mediated cytotoxicity (ADCC), cell migration, autophagy) and carry out repurposing drug library screens in these applications. One of our goals in the BenBedPhar project is to collaborate with partners on revealing potential overlaps between Nrf2 and PARylation signaling and to participate in HTS/HCS-based identification of novel Nrf2 modulator drugs.

László Virág is full professor at and head of the Department of Medical Chemistry, Faculty of Medicine, University of Debrecen, Hungary. He studies the molecular mechanisms involved in oxidative DNA damage signaling with special regard to the role of protein PARylation. In recent years his research focused on the following lines of activity:
i) how do macrophages protect themselves from PARylation-dependent cell death (parthanatos);
ii) how PARylation regulates macrophage polarization in cancer;
iii) how cancer cell-immune cell interactions can be pharmacologically modulated.