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Live or Die: PD-L1 delays neutrophil apoptosis

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In this issue of Blood, Wang et al. uncover a key role for programmed death ligand 1 (PD-L1), which delays neutrophil apoptosis at the inflammatory site through activation of the PI3K-AKT survival pathway¹.

Polymorphonuclear neutrophils (PMN) are the most abundant circulating leukocytes, constituting 60 to 70% of circulating white blood cells. PMN are terminally differentiated and have a short life span, but are essential for innate immunity and host defense against microbes². They are the first cells to migrate out of the circulation and to be massively recruited at the infection site where they recognize microbes *via* different receptors expressed at their cell surface, inducing engulfment of the microbe into a phagosome^{3,4}. Killing of microbes by PMN occurs through the release into the phagosome of highly toxic agents such as reactive oxygen species (ROS) and granule contents including myeloperoxidase, glucosidases, proteases and anti-bacterial peptides. Microbes can also be trapped and killed by neutrophil extracellular traps (NETs)⁵. Many processes such as apoptosis, NETosis, autophagy, pyroptosis, necroptosis and necrosis can induce the death of neutrophils⁵, upon which they are phagocytized and eliminated by local macrophages through a process called efferocytosis, resulting in the cleaning up of the infection site. Thus, PMN are critical anti-inflammatory components of the innate immune system as their physiological role is

to resolve both infection and inflammation. Nevertheless, excessively activated or delayed apoptosis, results in PMN becoming harmful to surrounding tissues due to cell injury and continued inflammatory reaction, the driving factors for inflammatory disorders such as rheumatoid arthritis, inflammatory bowel diseases, lung inflammation and sepsis⁴.

Tissue neutrophils are believed to have longer lifespan than circulating PMN, due to the presence of survival factors at the inflammatory site. Studies in animal models reported that delaying neutrophil apoptosis has a pro-inflammatory effect and extended neutrophil lifespan through apoptosis suppression was observed in patients with several inflammatory diseases and is associated with increased disease severity⁶. Neutrophils isolated from blood die through constitutive apoptosis, which can be either accelerated or inhibited by several agents. The best known neutrophil anti-apoptotic factors are G-CSF and GM-CSF. Inhibition of neutrophil apoptosis can contribute to inflammation; however, the factors leading to dysregulation of neutrophils apoptosis in inflammatory conditions are still not completely identified. In this issue of Blood, Wang et al.¹ demonstrate that PD-L1 plays a key role by delaying neutrophil apoptosis at the inflammatory site through the PI3K-AKT pathway (Figure 1).

Programmed cell death-1 (PD-1) protein, expressed on immune cells, is an immune checkpoint inhibitory receptor that triggers immunosuppressive signaling pathways⁷. PD-1 binds to PD-L1 or PD-L2 and blocks activating signals from T-cell receptors and CD28. PD-1/PD-L1 functions as brakes to limit the adaptive immune response, mainly the beneficial T-cell functions in cancer. PD-L1 is expressed at the plasma membrane of T-lymphocytes, B-lymphocytes and antigen-presenting cells and in some non-lymphoid tissues and non-immune cells⁷. Cancer cells also express PD-L1, which binds to T cell surface via PD-1 allowing them to escape host immune response. Thus, anti-PD-1/anti-PD-L1 antibodies have been used to treat various types of cancer. Previous studies from the same group and others have shown that PD-L1 expression on neutrophils increases in various inflammatory conditions^{8,9}. In this new study, Wang et al.¹

confirm previous findings and further show that PD-L1 overexpression in neutrophils from septic patients correlates with neutrophil survival. Silencing PD-L1 expression using siRNA accelerated apoptosis of septic neutrophils. Interestingly, neutrophils challenged with IFN- γ +LPS and neutrophils from septic patients exhibited increased AKT phosphorylation, which was reversed by PD-L1 siRNA. They revealed that PD-L1 co-immunoprecipitates with the p85 subunit of PI3K, the upstream regulator of AKT. *In vivo*, neutrophil PD-L1 deletion reduced neutrophil lung infiltration in a cecal-ligation and puncture murine model and attenuated lung injury. Thus, increased PD-L1 expression on human neutrophils during inflammation delays cellular apoptosis via PI3K-AKT pathway, driving lung injury and mortality.

The study by Wang et *al.* brings significant new information to the neutrophil field. The first important message is that PD-L1 is not only a key player in cancer immunomodulation, but also in inflammation, raising the possibility that it could be a novel pharmacological target and that antibodies to PD-L1 could be tested in inflammatory diseases. The second is that PD-L1 upregulation in neutrophils during inflammation and sepsis promotes their survival. The third is that it highlights the novel and important role of PD-L1 as an inducer of the PI3K-AKT signaling pathway, which regulates many neutrophil inflammatory functions. Thus, this study adds another critical step to our understanding of the neutrophil biology.

As it is always the case with novel mechanisms, it also raises several questions. In cancer and other cells, PD-L1 is expressed at the plasma membrane, but its localization in neutrophils is not addressed by the authors. It would be interesting to know whether it is expressed at the plasma membrane or at the membrane of neutrophil granules. Expression of PD-L1 at the plasma membrane would make it an easy target for immunotherapies with blocking antibodies. Indeed, while this study was under revision, Thanabalasuriar et *al.*¹⁰ reported the role of PD-L1+ neutrophils in airway inflammation in mice and showed that an anti-PDL1 antibody protected mice from inflammation.

Patera et al.⁹ have also shown that inflammatory neutrophils express PD-1, the intercellular PD-1/PD-L1 engagement on PMN could induce PI3K-AKT activation in neutrophils. This possibility could be checked using blocking antibodies.

Wang et al. showed that IFN- γ +LPS induced PD-L1 expression in neutrophils; however, it would be of interest to know whether other inflammatory stimuli such as TNF α , GM-CSF, IL-6, IL-8, etc also induce PD-L1 expression in PMN and by which mechanisms.

While this study suggests a fundamental role of the PI3K-AKT pathway in mediating PD-L1-induced neutrophil survival, the mechanism by which PD-L1 activates PI3K is not investigated as the authors only show its ability to bind p85-PI3K when over-expressed in HEK293 cells. This pathway should be checked in inflammatory neutrophils. In addition, the PI3K-AKT pathway could modulate several other important neutrophil functions including superoxide production, degranulation and chemotaxis, raising the question of whether these functions are also impacted in PD-L1+ neutrophils. Furthermore, it would be interesting to evaluate the role of PD-L1 in other human inflammatory diseases such as rheumatoid arthritis and inflammatory bowel diseases, and related mouse models of inflammation.

In summary, the work by Wang et al.¹ represents a major advance in our understanding of neutrophil biology. Notably, it uncovers the important function of the PD-L1-PI3K-AKT axis in delaying neutrophils apoptosis in inflammatory situations. This opens new avenues for novel therapeutic approaches in several immunological and inflammatory diseases and raises intriguing questions about PD-L1 to be explored by the neutrophil scientific field.

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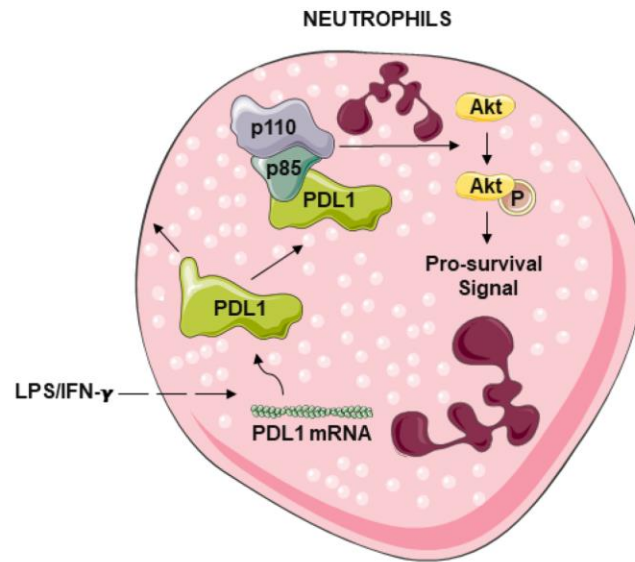


FIGURE 1. (Please use the corrected graphical abstract here). LPS+IFN γ and septic environment induce PD-L1 expression in human neutrophils. PD-L1 binds to p85, the PI3Kinase regulatory subunit, and PI3Kinase activates AKT kinase to induce pro-survival signals in neutrophils making them live longer.