Comment on Oliva et al, page 2132

The yin and yang of autophagy in AL amyloidosis

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MAYO CLINIC

In this issue of Blood, Oliva et al report on a series of experiments that have demonstrated that in systemic light chain (AL) plasma cells (PCs), there is a complex interaction between those PCs and the immunoglobulin light chains (LCs) they produce.1 The pathology introduced by these unstable amyloidogenic LCs occurs not only at distant organs2,3 but also in the plasma cells that produce them. This manuscript attempts to unravel the relationship of AL LCs and the PCs that produce them in the context of AL PC susceptibility to proteasome inhibitors and the role autophagy may play in that susceptibility.

Macroautophagy, or autophagy, is a coordinated catabolic process by which damaged and aged organelles and protein aggregates too large to be degraded by the ubiquitin-proteasome system are directed for lysosomal-mediated degradation (see figure panel A). Autophagy maintains organelle turnover and homeostasis. In addition to exerting control over cellular protein quality, autophagy is induced during nutritional deprivation, trophic factor withdrawal, and other types of cell stress to protect cells against apoptosis by degrading nonessential cell constituents for energy.4

The authors’ first observation is that AL PCs and multiple myeloma PCs both experience proteostatic stress as a result of their immunoglobulin production workload, but both types of PCs have similar proteasome capacity and workload.1 The higher sensitivity of AL PCs as compared with multiple myeloma PCs to a proteasome inhibitor appears to have less to do with their respective proteasome capacity (load vs capacity) than with their reduced autophagic control of organelle homeostasis. Using multiple myeloma PCs as controls, the authors demonstrate that in AL PCs, both the increased need for autophagy (as a result of endoplasmic reticulum stress and mitochondrial stress) and their autophagic impairment appear to be in part a result of the toxic AL LCs.

Mechanistically, these authors’ observations partially depart from other reports in the literature. The authors conclude that the abundant ER- and mitochondria-containing autophagosomes in AL PCs are a function of increased autophagy and/or of decreased lysosomal digestion of these autophagosomes, but favor the former as an explanation based on morphologic data.1 In contrast, in other models, data would point to diminished clearance/decreased lysosomal digestion as the major source of increased cellular autophagosomes.2,4 More work will be required in AL PCs to make this distinction.

Most important, the authors’ observations in AL PCs introduce a paradox for how one can translate their observations into treatment strategies for patients with AL amyloidosis. The same dysregulation of autophagy that makes AL PCs more sensitive to proteasome inhibitors and the role autophagy may play in that susceptibility.

(A) Autophagy. An isolation membrane engulfs cytoplasm or organelle to form a double-membrane cytosolic vesicle referred to as an autophagosome. This autophagosome fuses with a late endosome or a lysosome to form an autophagolysosome. Inside the autophagolysosome, the lysosomal hydrolyses degrade the sequestered material, which then becomes available to the cell for recycling. (B) Similar processes in plasma cells1 and cardiomyocytes2 have net opposing effects for the patient. Amyloidogenic immunoglobulin light chain induced dysregulated autophagy in a malignant PC favors cell death, which is good for the patient. In contrast, dysregulated autophagy in a cardiomyocyte also favors cell death, which is bad for the patient. ER, endoplasmic reticulum.
inhibition and contributes to impaired proliferation of AL PCs is a similar type of dysregulation of autophagy that others have demonstrated to be the source of toxicity in cardiomyocytes. For the AL PC, the goal would be to enhance (or perhaps merely to exploit) this impairment of autophagy; however, for organs the LCs target, such as the heart, the goal would be to enhance autophagy (see figure panel B). Clinical investigators are left with the question of whether autophagy activators such as rapamycin would be friend or foe: friend to the cardiomyocyte and the malignant plasma cell, but foe to the mission of eradicating the PC clone. Would one dare try an inhibitor of autophagy such as hydroxychloroquine to increase PC death for fear of decompensating a patient’s AL-involved heart further? Could some of the purported cardiac toxicity observed in some patients with AL amyloidosis treated with proteasome inhibitors be in part a result of this same mechanism?

Oliva and colleagues answer several interesting questions about the mechanisms of PI-induced AL PC death and the general processes occurring within these cells. Moreover, they offer an inducible in vitro murine PC model to further study these interactions of AL LCs in PCs and to potentially identify effective treatment strategies. This manuscript, taken in the context of the literature, however, is a potent reminder of the yin and yang of chemotherapy for patients with AL amyloidosis. It is well known that therapeutic indices are typically narrower in patients with AL amyloidosis treated with proteasome inhibitors be in part a result of this same mechanism?

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REFERENCES

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LYMPHOID NEOPLASIA

Comment on Dalla Pria et al, page 2143

HIV multicentric Castleman: rituximab sans maintenance

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Whether maintenance therapy adds value in the treatment of HIV-associated multicentric Castleman disease (HIV+MCD) is unknown. In this issue of Blood, Dalla Pria et al have analyzed a prospective cohort to advocate that it is not.1

MCD is a potentially fatal systemic illness highly associated with HIV infection. In the setting of HIV, human herpesvirus 8 (HHV8) plays a critical role2 with the latent nuclear antigen-1 (LANA-1) expressed in the plasmablasts found within the B-cell follicles of pathologically enlarged nodes. Not a true malignancy, these plasmablasts are polyclonal, though monotypic for immunoglobulin M-κ.3,4 Despite the fact that the plasmablasts express only low levels of CD20,5 rituximab (the monoclonal antibody directed against CD20) induces complete remissions,6,7 likely by destroying the B cells elaborating interleukin-6 leading to the pathophysiology.8 With rituximab survival rates at 5 years improved from 33% to 90%.9

Despite this success, MCD is a relapsing illness in some patients. Because relapse can lead to death, some have advocated maintenance therapy.10 It is difficult to assess the efficacy of this strategy as the rate of relapse and the efficacy of rituximab reinduction are unknown. Maintenance therapy is costly financially, inconvenient (IV), and associated with hypogammaglobulinemia in already immunocompromised patients.

To address this, Dalla Pria et al evaluated a prospective database of 84 HIV+MCD patients treated at Chelsea and Westminster Hospital (London, United Kingdom) since 2003. Notably, both initial and relapse disease were biopsy proven. This is important in a disease whose presentation overlaps with

Kaplan-Meier curve showing the OS of 84 patients treated with rituximab-based immunotherapy for HIV+ MCD. See Figure 2 in the article by Dalla Pria et al that begins on page 2143.
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