● ● ● **NEOPLASIA**

Comment on Arimura et al, page 661

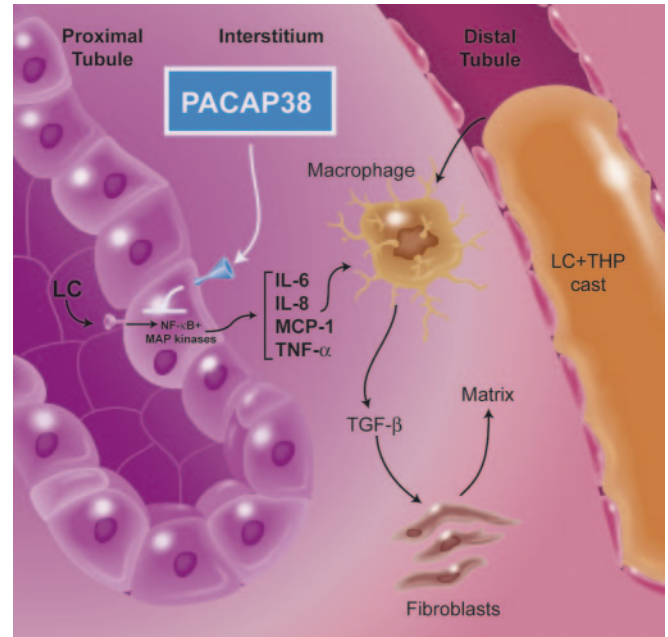# A new twist in myeloma treatment

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Renal failure in multiple myeloma complicates treatment and shortens life span. Arimura and colleagues introduce the concept that a member of the vasoactive intestinal peptide family might serve a potential renoprotective role in cast nephropathy.

One of the severe and common complications of multiple myeloma is renal failure. The underlying etiology is cast nephropathy, also known as myeloma kidney, in more than two thirds of myeloma-associated renal diseases. The central feature of this process is the immunoglobulin light chain, which is a low-molecular-weight protein that readily undergoes glomerular filtration and can appear in the tubular lumen in significant concentrations, particularly in the setting of multiple myeloma. A prominent feature of cast nephropathy is tubulointerstitial fibrosis, which involves 2 processes (see figure). Proximal tubular reabsorption of light chains sparks the activation of NF-κB and mitogen-activated protein (MAP) kinases; these signaling pathways cooperate to promote chemokine and cytokine production by these cells.[1,2] Intrarenal production of these agents facilitates the infiltration of inflammatory cells, which in turn increase TGF-β production, resulting in renal interstitial matrix protein deposition. The second process involves coprecipitation of the light chain in the distal nephron with Tamm-Horsfall protein,[3,4] a secreted and apically anchored glycoprotein synthesized by cells of the thick ascending limb of the loop of Henle. Cast formation in the distal nephron obstructs the flow of tubular fluid and promotes breaks in the epithelial lining, facilitating interstitial inflammation. It is likely that both processes contribute to the interstitial fibrosis of cast nephropathy.

In this issue of *Blood*, Arimura and colleagues extended their earlier observations involving proximal tubular epithelial cell activation by light chains, by identifying a novel inhibitor of cytokine production. The investigators demonstrated that pituitary adenylate cyclase-activating polypeptide with 38 residues (PACAP38), a member of the vasoactive intestinal peptide family, effectively inhibited signal transduction events and associated secretion of IL-6 and TNF-α mediated by incubation of a human proximal tubule cell line with a human immunoglobulin light chain. Furthermore, the inhibitory effect of PACAP38 on light chain–induced renal production of TNF-α was demonstrated in vivo in rats. Because PACAP38 also inhibited in vitro light chain–mediated epithelial cell injury and suppressed growth of myeloma cells, the authors concluded that PACAP38 therapy might serve as a renoprotective agent in multiple myeloma.

Of clinical importance is the observation that cast nephropathy represents a potentially reversible form of renal failure. More importantly, early identification and treatment may prevent the progression to end-stage kidney failure commonly seen in cast nephropathy. By decreasing the circulating levels of monoclonal light chain, cytoreduction therapies are mainstays of treatment. However, eradication of

Following glomerular ultrafiltration, immunoglobulin light chains (LCs) bind to a receptor on the apical surface of proximal tubule epithelial cells and undergo endocytosis. Through a process not yet understood, NF-κB and the MAP kinase pathways are activated, resulting in production of chemokines and cytokines that include IL-6, IL-8, MCP-1, and TNF-α. Local production of these chemoattractants results in renal interstitial inflammation, TGF-β activation, and matrix protein production by fibroblasts. In the distal nephron, LC coprecipitates with Tamm-Horsfall protein (THP) to produce an intraluminal cast that obstructs tubule fluid flow and produces breaks in the epithelial cell lining, compounding the interstitial scarring. PACAP38 prevents the activation of the proximal tubule epithelium by LC and inhibits production of TNF-α and IL-6. Illustration by A. Y. Chen.

the clone of plasma cells can be challenging, and circulating (and potentially nephrotoxic) light chains often remain detectable for some time after initiation of therapy. While additional studies are required, the original findings of Arimura and associates have merit and support a potential role for PACAP38 as adjunctive therapy in myeloma with associated cast nephropathy.

Dr Sanders is supported by the Medical Research Service of the Department of Veterans Affairs and by a grant from the Multiple Myeloma Research Foundation. ■

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● ● ● ● **HEMOSTASIS** ▬▬▬▬▬

Comment on Crawford et al, page 566

No kidding! Hemoglobin makes NO

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Crawford and colleagues suggest that hypoxic red blood cells mediate vasodilatation by reducing circulating nitrite anions to nitric oxide.

Regulation of microcirculation is a dynamic process in which the need of the tissues is communicated to the vasculature, enabling the appropriate matching of oxygen supply to demand. A hypothesis has been put forward claiming that red blood cells (RBCs) sense hypoxia and then mediate an instantaneous vasodilatory response.[1,2] In this process, the unloading of oxygen from hemoglobin (Hb) is coupled to the release of a vasodilator from RBCs. The primary candidates for mediating red cell–induced vasodilation are ATP and NO. Stamler and colleagues (Jia et al[2]) originally suggested a role for a thiol (SH) group in Hb as a carrier and releaser of NO. According to this theory, the binding (formation of S-nitrosohemoglobin, SNOHb) and release of NO from Hb are allosterically regulated so that NO release occurs when Hb is deoxygenated.[2]

We have suggested a physiologic role for the nitrite anion (NO_2^-) in NO–mediated metabolic vasoregulation.[3,4] This involves NO synthase–independent reduction of nitrite to NO, a reaction that is greatly enhanced under hypoxic/ischemic conditions. Cosby et al elegantly expanded on this and showed that nitrite is reduced to vasodilatory NO in vivo by deoxyhemoglobin in RBCs.[5] In this issue of *Blood,* Crawford and colleagues have carefully examined the role of RBCs and hemoglobin in relation to hypoxic vasodilatation. In their interesting study, they report that RBCs handle nitrite differently depending on the Hb oxygen saturation. When Hb is fully oxygenated, the primary reaction is oxidation of nitrite into biologically inert nitrate. As oxygen saturation falls along the vascular tree, Hb gradually turns into a "reductase" and starts to reduce nitrite into vasodilatory NO. The maximal nitrite reduction is observed when Hb is approximately 50% oxygenated (P_{50}). According to the authors, this is ideal for the purpose of hypoxic vasoregulation, as 50% oxygenation prevails in the critical arterioles where blood flow and oxygen delivery is controlled.

Of interest, the physiologic effects of nitrite seem to extend beyond regulation of blood flow.[6] In heart and liver tissue, nitrite protects against ischemia-reperfusion injury, and in the gastric mucosa it serves protective functions via acidic reduction to NO. To better understand the overall physiology of nitrite, we need to carefully examine its origin. An obvious source is the NO synthases, given that nitrite is a major oxidation product of NO. In addition to this, the diet is also a large contributor to systemic nitrite levels mainly via bioconversion of dietary nitrate (found mainly in vegetables) to nitrite.[6] This implies that the physiologic regulatory role of nitrite described here and elsewhere is influenced by what we eat. Thus, ingestion of nitrate-rich food results in a build-up of "nitrite reserves" to be used in critical situations of hypoxia.

There is an intense ongoing debate as to which pathway for NO formation by RBCs is the most significant: the SNOHb pathway or the nitrite pathway. The SNOHb theory has been questioned lately mainly because many groups have been unable to detect SNOHb in human blood. Crawford and colleagues now convincingly show that at least nitrite reduction to NO does not require SNOHb as an intermediate. An inherent problem with both models is the mechanism by which NO is released from RBCs. How can NO escape without being captured and destroyed by the abundant oxyHb? The present study nicely demonstrates NO gas formation from hypoxic RBCs and nitrite (albeit at unphysiologically high concentrations) and with maximum levels obtained at the P_{50}. Nevertheless, I believe the final piece of evidence for a role of red cell–derived NO in physiologic regulation of blood flow is still lacking. What we need now is for different laboratories to start pulling together to design the missing crucial in vivo experiments. Nevertheless, it is a truly fascinating story we are witnessing. In just one decade, Hb has gone from being merely a NO scavenger to NO carrier and now NO generator. ■

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