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Role of PAPP-A in Aging and Age-related Disease

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Abstract

As suggested by its name, pregnancy-associated plasma protein-A (PAPP-A) plays an important role in pregnancy and fetal development (Lin et al., 1974; Brizot et al., 1996; Smith et al., 2002). On the opposite end of life's spectrum, recent studies using genetically-engineered mice indicate a newly recognized role for PAPP-A in aging and in the development of age-related disease. These latter studies will be reviewed in this article.

Keywords

Pregnancy-associated plasma protein-A; Insulin-like growth factors; Atherosclerosis; Aging

1. PAPP-A AND ITS REGULATION

Early studies identified PAPP-A as a novel zinc metalloproteinase that regulates the local bioavailability of insulin-like growth factors (IGF-I and -II) through cleavage of specific proteins that bind IGF and prevent ligand interaction with specific transmembrane IGF receptors (reviewed in Boldt and Conover, 2007). In this way PAPP-A can enhance the diverse effects of IGFs on cell proliferation, survival, and differentiated function. PAPP-A is expressed in a variety of tissues and cell types, and is potently up-regulated by pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-α and interleukin (IL)-1β (Resch et al., 2004; Conover et al., 2008). This stimulation of PAPP-A expression by pro-inflammatory cytokines may explain the induction of PAPP-A associated with dermal myofibroblasts in healing human skin (Chen et al. 2003). Furthermore, chronic high level expression of TNF-α and IL-1β by activated macrophages may contribute to pathological overexpression of PAPP-A in human atherosclerotic plaque formation (Conover et al., 2007). Chronic low level inflammation associated with aging may also impact PAPP-A expression, although this regulation has not been directly addressed.

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2. PAPP-A AND ATHEROSCLEROSIS

We first investigated a possible role for PAPP-A in atherosclerosis because IGF-I is known to play a role in the vascular injury response, PAPP-A is expressed by arterial smooth muscle and endothelial cells in response; to TNF-α and IL-1β *in vitro*; and PAPP-A is highly expressed in unstable, but not stable, atherosclerotic plaque in humans (Conover et al., 2006; Conover et al., 2008; Bayes-Genis et al., 2001). In addition, elevated circulating levels of PAPP-A have been found in patients at risk for adverse cardiac events in numerous clinical studies (Bayes-Genis et al., 2001; Lund et al., 2003; Iversen et al., 2011). To determine whether inhibition of PAPP-A would alter the development of atherosclerotic plaques, we created PAPP-A knock-out (KO) mice and cross-bred them with apolipoprotein E (ApoE) KO mice, the latter being a mouse model of atherosclerosis. ApoE KO and ApoE KO/PAPP-A KO mice were fed a high fat diet starting at 7 weeks of age, and aortic lesions assessed after 5, 10 and 20 weeks on the diet (Harrington et al., 2007). ApoE KO mice showed marked progression of aortic plaque size and complexity over time with high fat feeding. Although cholesterol and triglyceride levels were elevated to the same extent in both groups of mice, there was little increase in plaque size in ApoE KO/PAPP-A KO mice between 5 and 20 weeks, resulting in 70–80% reduction in aortic lesion area compared to ApoE KO mice. Lesion number, on the other hand, was the same in both groups of mice, indicating a role for PAPP-A in the progression but not the initiation of atherosclerotic plaque. Interestingly, the absolute quantity of macrophage staining was similar in both groups, suggesting that removal of PAPP-A as a target of macrophage-derived cytokines may be key in restraining plaque development. In support of PAPP-A having a direct effect on atherosclerotic plaque development, overexpression of PAPP-A in arterial smooth muscle resulted in enhanced aortic plaque development in ApoE KO mice (Conover et al., 2010).

3. PAPP-A AND AGING

Our next set of experiments employed PAPP-A KO mice to investigate PAPP-A and aging. So why might we expect PAPP-A to play a role in aging? There is plenty of evidence that IGFs are involved in aging and age-related diseases, and reduced IGF receptor signaling in species ranging from worms to mice is associated with healthy longevity (Kenyon, 2001). Since PAPP-A enhances IGF available for receptor signaling, we tested the hypothesis that loss of PAPP-A would extend lifespan in PAPP-A KO mice. Indeed, PAPP-A KO mice lived 30–40% longer than wild-type littermates; both median and maximal lifespan were significantly increased (Conover et al., 2010).

To answer the question of what contributes to PAPP-A KO mortality, we set up another aging study using a large number of wild-type and PAPP-A KO mice wherein both end-of-life and scheduled sacrifice histopathology was determined by expert veterinary pathologists (Conover et al., 2010). Again, PAPP-A KO mice had significantly extended longevity. Interestingly, approximately 30% of PAPP-A KO mice but only 6% of wild-type mice died without histological evidence of lethal pathological changes. Although the absolute incidence of neoplasia was not reduced in PAPP-A KO mice at the end of life, there was a significant delay in occurrence of presumably fatal neoplastic disease compared with wild-type mice. Reduction in age-related degenerative diseases also appeared to contribute to the extended lifespan in PAPP-A KO mice. Overall disease burden was significantly higher in wild-type than in PAPP-A KO mice.

To determine whether this extension of lifespan in PAPP-A KO mice was accompanied by improvement in heath during aging, comprehensive pathology was performed on wild-type and PAPP-A KO mice at 78, 104, and 130 weeks of age. In general, wild-type mice had more age-related degenerative lesions and tumors and an earlier onset of these changes than

PAPP-A KO mice. In particular, cardiomyopathy, nephropathy, neurodegenerative lesions, and testicular, ovarian and thymic atrophy were more evident and more severe in wild-type than PAPP-A KO mice at 78 and 104 weeks of age. Too few wild-type mice were available at 140 weeks for meaningful comparisons to PAPP-A KO mice. In an earlier study, we documented a resistance to thymic involution and maintenance of youthful T-cell phenotype in 78 week old PAPP-A KO mice (Vallejo et al., 2009), which may contribute to the delayed occurrence of neoplasia in PAPP-A KO mice. Overall, survival curves and pathology indicate an extended healthy lifespan of PAPP-A KO mice. These descriptive studies will be followed up with more focused mechanistic studies of PAPP-A in the heart, kidney, brain and the immune system.

4. PAPP-A AND CANCER

The delayed occurrence of spontaneous age-related tumors, primarily lymphomas, in PAPP-A KO mice may be more related to effects on the immune system than to direct PAPP-A regulation of IGF-stimulated tumor growth. We were interested in whether PAPP-A would have an effect on IGF-responsive tumors have an increased incidence in older adults, e.g., breast, ovarian, prostate, or colon cancer. To this end, we used an ovarian cancer cell line, SKOV3, that has low tumorigenic potential. Xenografts of SKOV3 clones transfected with and stably expressing full-length PAPP-A or empty vector control were made in nude mice (Boldt and Conover, 2011). Control SKOV3 clones showed little, if any, tumor take/growth over 6 months, whereas tumors from the clones over-expressing PAPP-A appeared within 2 or 3 months and rapidly progressed to endpoint, as defined by tumor burden of 10% by weight. Expression levels of IGF system components indicated the potential for PAPP-A regulation of IGF-stimulated growth. Unpublished data demonstrated that an inhibitor of IGF-I receptor signaling could suppress tumor growth in the SKOV3 cells overexpressing PAPP-A.

5. CONCLUSIONS

There are now strong data supporting a role for PAPP-A in aging and age-related diseases, such as atherosclerosis and cancer, with implications for PAPP-A as a potential therapeutic target.

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ABBREVIATIONS

PAPP-A	pregnancy-associated plasma protein-A
IGF	insulin-like growth factor
IL	interleukin
TNF	tumor necrosis factor
ApoE	apolipoprotein E
KO	knock-out

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HIGHLIGHTS

- Pregnancy associated plasma protein-A (PAPP-A) is a novel zinc metalloproteinase that enhances local bioavailability of the insulin-like growth factors
- PAPP-A expression is stimulated by proinflammatory cytokines
- PAPP-A plays a role in the progression of atherosclerotic plaque development
- Mice null for PAPP-A have extended healthy lifespan
- Overexpression of PAPP-A promotes tumor growth