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Dynamic aspects of the gene expression in the testis during its atrophy

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Although reactive oxygen species (ROS) underlie the pathogenesis of various diseases, they also play critical roles in the regulation of the redox balance required for physiological processes. Although possible involvement of ROS in the pathogenesis of di(2-ethylhexyl) phthalate (DEHP)-induced atrophy of rat testis has been suggested, the molecular mechanism of this phenomena has not been elucidated.

We previously investigated the gene expression for phospholipid hydroperoxide glutathione peroxidase (PHGPx) in rat testes by in situ hybridization. PHGPx mRNA was expressed stage-specifically during spermatogenesis in adult rats. Its expression first appeared in stage Ⅶ pachytene spermatocytes and markedly in spermatids between steps 7 and 12. Mitochondrial PHGPx plays an important role in the regulation of the mitochondria-dependent pathway of apoptosis. Hypophysectomy decreases PHGPx level in the testis and induces the degeneration of germ cells in rat seminiferous tubules around stage Ⅶ.

The research focused on changes in the gene expression in the testis in animals that received either hypophysectomy (10-week rats, 5.5 days after the operation) or DEHP administration (35-day rats, 2g/kg); both conditions induced the degeneration of germ cells. The expression of several genes, including lipid-binding protein (TLBP), markedly decreased in the testis of both groups as analyzed by cDNA microarray. However, ISH study did not show a decrease proportional to the results of the gene expression obtained by cDNA microarray. Based on these observations, the usefulness of cDNA microarray in detecting critical molecules in the pathogenesis of testis atrophy will be discussed.

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Pathogenomics of a multifactorial disease: Lessons from an MRL/lpr mouse model

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Recent advances in genomics of human and mouse can be expected to clarify the genetic inheritance of multifactorial diseases and to identify their susceptibility genes by using murine models. Collagen disease has been considered to be a representative one of multifactorial diseases, which is a syndrome of three overlapping disease categories; connective tissue disease, rheumatic disease and autoimmune disease, involving systemic lupus erythematosus, rheumatoid arthritis, polyarteritis nodosa, Sjogren's syndrome, etc. However, their pathological findings show complex lesions such as glomerulonephritis, vasculitis, arthritis, and/or sialoadenitis, etc. Thus, it is still controversial whether such diversity and similarity of pathological manifestations among the collagen disease depends on ambiguity in diagnosis or is an intrinsic quality of the diseases themselves. An MRL/Mp-*lpr/lpr* (MRL/lpr) strain of mice shows various forms of collagen disease, including glomerulonephritis, vasculitis, polyarthritis and sialoadenitis. On a series of our genetic studies with total genome analyses of MRL/lpr mice, we identified the susceptibility loci to each lesions to point out the significance of polygenic inheritance in collagen disease. Then, it allows us to conclude that the diversity and similarity of the pathological manifestations among various disease categories in collagen disease will be a result of the combination of polygenes. These genes, including both susceptible and resistant ones, may regulate cascade reactions leading to the pathological manifestations via the expression of functional proteins which differ quantitatively and/or qualitatively based on allelic polymorphism. Further identifying human candidate genes may improve the diagnostic criteria and categorization of collagen diseases should provide promising clues for determining the prognosis of patients with collagen disease.

References

1.Nose M, et al. *Am J Pathol* 149:1763-69, 1996.
2.Nishihara M, et al. *Arthritis Rheum* 42:2616-23, 1999.
3.Qu WM, et al. *Eur J Immunol* 30:2027-37, 2000.
4.Nose M, et al. *Int Rev Immunol* 19:473-98, 2000.
5.Kamogawa J, et al. *Arthritis Rheum*, in press.