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ORIGINAL ARTICLE

Prostate anatomy in motheaten viable (*me^v*) mice with mutations in the protein tyrosine phosphatase SHP-1☆

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Abstract

Objective: To study prostate and seminal vesicle anatomy in viable motheaten (*me^v*) mice with mutations in the PTPN6 gene leading to a severe reduction in the activity of protein tyrosine phosphatase SHP-1. Homozygous *me^v* mice exhibit multiple anomalies that include immunodeficiencies, increased proliferation of macrophage, neutrophil, and erythrocyte progenitors, decreased bone density and sterility.

Materials and methods: We analyzed macro- and microscopic anatomy of the seminal vesicle and prostate macro- and microscopic anatomy of 5 *me^v*/*me^v* and 8 *wt*/*wt* adult 7-week-old mice. Computerized morphometric analysis was performed to measure the relative changes appearing in the epithelial volume of the different prostatic lobes.

Results: All mice studied revealed normal genital organs (penis, testis, epididymis, vas deferens) and bladder. The seminal vesicle was absent in all *me^v*/*me^v* individuals analyzed, being normal and very noticeable in wt/wt mice. The different glands that compose the prostatic complex (anterior, ventral and dorso-lateral prostate) were atrophied in *me^v*/*me^v* mice: anterior prostate 0.4 times, ventral 0.19 times, dorsal 0.35 times and lateral 0.28 times those of the respective regions in wt/wt mice. Microscopically, *me^v*/*me^v* mice revealed scarce and large prostatic ducts, acini severely atrophic with empty lumen and scarce loose epithelial component forming tufts and infoldings, and hyperplastic changes in fibromuscular stroma.

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Conclusions: The prostate of me^v/me^v mice exhibits signs of aberrant differentiation and the resulting phenotype may be related to the loss of function of SHP-1. Prostatic anomalies in these mice affect, together with defects in sperm maturation, their sterility. These data suggest that SHP-1 plays an important role in prostate epithelial morphogenesis.

PALABRAS CLAVE
Próstata;
Anatomía;
Diferenciación;
SHP-1;
Ratón *motheaten viable*

Anatomía de la próstata en ratones *motheaten viable* (me^v) con mutaciones en el gen de la proteína tirosina fosfatasa SHP-1

Resumen

Objetivo: Estudiar la anatomía de la próstata y la vesícula seminal en ratones *motheaten viable* (me^v) con mutaciones en el gen PTPN6 que conlleva una severa reducción en la actividad de la proteína tirosina fosfatasa SHP-1. Los ratones me^v homocigotos muestran múltiples anomalías que incluyen inmunodeficiencias, aumento en la proliferación de macrófagos, neutrófilos y progenitores de eritrocitos, disminución de la densidad ósea y esterilidad.

Material y método: Se analizó la anatomía macro y microscópica de la vesícula seminal y de la próstata, tanto a nivel macro como microscópico, de 5 ratones me^v/me^v (homocigotos me^v) y 8 ratones *wt*/*wt* (tipo salvaje) adultos de 7 semanas. Se ha realizado análisis morfométrico computarizado para medir cambios relativos en el volumen epitelial de los diferentes lóbulos prostáticos.

Resultados: Todos los ratones estudiados mostraron órganos genitales (pene, testículos, epidídimos, deferentes) y vejiga normales. La vesícula seminal se encontraba ausente en todos los ejemplares me^v/me^v analizados, siendo normal y muy llamativa en ratones *wt*/*wt*. Las diferentes glándulas que componen el complejo prostático (próstata anterior, ventral y dorsolateral) se encontraron atróficas en ratones me^v/me^v: próstata anterior 0.4 veces, ventral 0.19 veces, dorsal 0.35 veces y lateral 0.28 veces el tamaño de las respectivas regiones en ratones *wt*/*wt*. A nivel microscópico los ratones me^v/me^v mostraron ductos prostáticos mayores y escasos, acinos severamente atróficos con luces vacías y escaso y suelto componente epitelial formando penachos y pliegues, y cambios hiperplásicos en el estroma fibromuscular.

Conclusiones: La próstata de ratones me^v/me^v muestra signos de diferenciación aberrante y el fenotipo resultante puede estar relacionado con la pérdida de función SHP-1. Las anomalías prostáticas en estos ratones influyen, junto con los defectos de la maduración espermática, en su esterilidad. Estos datos sugieren que SHP-1 desempeña un importante papel en la morfogénesis epitelial prostática.

Introduction

Phosphorylation is one of the main changes that proteins undergo after being synthesized. It has been estimated that between 30 and 50% of the proteins in eukaryotic organisms can be phosphorylated. This change is directly involved in the control of different cellular processes such as: migration, proliferation, apoptosis, differentiation, metabolism, immunity, learning, and memory. Therefore, it is not surprising that changes in protein phosphorylation patterns have been associated with cancer, diabetes, and inflammatory and neurodegenerative illnesses.[1] The phosphorylation level of a protein is the result of the activity of 2 types of enzymes: protein kinases in charge of phosphorylation and protein phosphatases responsible for dephosphorylation.

Within the phosphatase group is the SHP-1 protein, codified by the *PTPN6*[2] gene, which is mainly expressed in hematopoietic and epithelial cells. The existence of 2 strains of mice with mutations affecting this phosphatase gene has enabled us to know its regulatory role. These 2 strains are called *motheaten (me)*[3] and *motheaten viable* (me^v).[4] Their genetic analysis has revealed that those *me* mice lacked SHP-1, whereas the me^v ones expressed a deficient form of the enzyme with an activity of 20%.[5,6] The homozygous mice (*me*/*me* or me^v/me^v) showed hematopoietic abnormalities which considerably shortened their lives (2 to 3 weeks for the former ones and 9 to 12 for the others). These mice suffered from extramedullary hematopoiesis, splenomegaly, dermatitis, and hemorrhagic pneumonitis. Alterations of the lymphoid ontogeny were observed, which led to chronic inflammations and a picture of systemic autoimmune disease evidenced by hypergammaglobulinemia, the presence of autoantibodies and tissue damage caused by the presence of circulating immune complexes. Natural killer (NK) lymphocytes and cells of the erythroid line were also altered. The analysis of all these alterations, obviously due to the absence or defect in SHP-1, has demonstrated that this phosphatase is a negative regulator of multiple signals in hematopoietic cells, including those activated by interleukins, growth factors, adhesion and immunoreceptors[7] and it has enabled us to classify SHP-1 as a potential tumor suppressor gene. Loss or reduction of SHP-1 has also been observed in various kinds of lymphomas