Ganglion cell-like (GL) cells reside in the dermis of the ventral skin of mature male Djungarian hamsters (*Phodopus sungorus*) and express androgen receptor (AR). To assess whether GL cells have androgen-dependent behavior, we evaluated the histologic changes of GL cells after gonadectomy. Five male and 5 female hamsters were gonadectomized at the age of 4 wk and necropsied 14 wk later. The number, distribution, and proliferative activity of GL cells in the thoracoabdominal and dorsal skins were evaluated histologically and compared with those of corresponding intact animals. GL cells were more numerous, were distributed throughout the skin more widely, and had higher proliferative activity in the intact male hamsters than in their gonadectomized counterparts. Similar trends regarding these 3 parameters were seen in ovariectomized compared with intact female hamsters and between intact male and intact female hamsters. These results suggest that the GL cells of Djungarian hamsters demonstrate sex-associated differences in their distribution and proliferative activity and that androgen may be involved in the development of these cells.

**Abbreviations:** AR, androgen receptor; GL cell, ganglion cell-like cell.

Ganglion cell-like (GL) cells reside in the dermis of the abdominal and thoracic skin of mature male Djungarian hamsters (*Phodopus sungorus*). GL cells have a small round nucleus with an apparent nucleolus and abundant basophilic foamy cytoplasm. These cells usually aggregate to form nests accompanied by various volumes of stromal collagen fibers. The nests increase in size and number with maturation. The nuclei of GL cells have a positive reaction for androgen receptor (AR), and the cytoplasm is positive for vimentin. Although the morphologic characteristics and various immunophenotypes of GL cells have been documented, their behavior and role remain almost unclear. Some authors speculate that increased levels of testosterone may influence GL cell proliferation and the oncogenesis of atypical skin fibromas preferentially arising in this species.

The current study aims to elucidate the androgen-dependent behavior of GL cells and compare the histologic changes of GL cells in gonadectomized Djungarian hamsters with those in intact control animals.

**Materials and Methods**

**Animals.** Male and female Djungarian hamsters (age, 4 wk; Saitama Experimental Supply, Sugito, Japan) were kept in aluminum press cages (22 cm × 32 cm × 11 cm; Tokiwa Kagaku Kikai, Tokyo, Japan) containing corncob bedding (Green-Tru, Green Products, Conrad, Iowa) under a controlled environment maintained at 22 ± 1.5 °C, with 50% ± 20% relative humidity and 12:12-h light-dark cycles and had unrestricted access to pelleted food (NMF, Oriental Yeast, Tokyo, Japan) and tap water. Hamsters were housed as 1 pair per cage for mating. All pups were kept under similar conditions. Breeding was repeated as needed to obtain the number of animals necessary for this experiment. Serologic monitoring against specific pathogens was performed every 6 mo by using Djungarian hamsters housed in the same animal room as the study population. The most recent results confirmed the lack of serum antibodies against *Clostridium piliforme*, *Mycoplasma pulmonis*, Sendai virus, and mouse hepatitis virus. Hamsters were also free of *Pseudomonas aeruginosa*, *Salmonella* spp., *Pasteurella pneumotropica*, *Citrobacter rodentium*, *Corynebacterium kutscheri*, *Citrobacter rodentium*, *Corynebacterium kutscheri*, *Mycoplasma* spp., *dermatophytes*, *Giardia* spp., *Spironucleus muris*, and *Syphacia* spp.

The study hamsters (*n* = 10 per sex) were allocated into a gonadectomized group (5 male, 5 female) and an intact group (5 male, 5 females); 2 or 3 animals from the same group and sex were housed together. For gonadectomy, the animals were injected with pentobarbital sodium (32.4 mg/kg IP; Kyoritsu Seiyaku, Ltd., Tokyo, Japan) and anesthetized, the testes and ovaries were removed aseptically, and the skin incisions were swabbed with 80% ethanol after suturing.

All animals were euthanized by pentobarbital overdose at 18 wk of age, and the thoracoabdominal and dorsal skins were collected. All experimental procedures were approved by the Animal Care and Use Committee of the University of Miyazaki.
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Cells was concentrated at the middle zone of the ventral skin. In intact male hamsters, GL cells were most numerous and showed the widest distribution: they occurred throughout the ventral skin as well as in some dorsal skin strips (Figure 2). In comparison, intact female and castrated male hamsters had considerably fewer GL cells, which were restricted to the ventral skin (as for ovariectomized females) than did intact males. The GL cell grade (mean \( \pm SD \)) of intact male hamsters (1.83 \( \pm 0.15 \)) was significantly (\( P < 0.05 \))

**Results**

**Histologic evaluation of growth of GL cells.** GL cells were found in all groups of hamsters regardless of sex, although they differed in number and distribution between groups. The population of GL cells was concentrated at the middle zone of the ventral skin. In intact male hamsters, GL cells were most numerous and showed the widest distribution: they occurred throughout the ventral skin as well as in some dorsal skin strips (Figure 2). In comparison, intact female and castrated male hamsters had considerably fewer GL cells, which were restricted to the ventral skin (as for ovariectomized females) than did intact males. The GL cell grade (mean \( \pm 1 SD \)) of intact male hamsters (1.83 \( \pm 0.15 \)) was significantly (\( P < 0.05 \))
Androgen-dependent behavior of skin ganglion cell-like cells from GL cells. In addition to the marked sex-associated difference in GL cell distribution, the PCNA index of the GL cells and thus their proliferative capacity was higher in the intact male hamsters than in the intact females. A similar trend in the PCNA index of GL cells has been reported previously.7

In the castrated male hamsters, the GL cell number, distribution, nest size, and PCNA index were clearly lower than those in the intact males. Therefore, gonadectomy decreased the proliferative activity of GL cells, leading to their restricted distribution. The primary hormonal change induced by male gonadectomy is thought to be a decrease in serum androgen concentration in humans12 and several other species.4 Most of the biologic effects of androgens are mediated by AR, which activates downstream androgen-dependent signaling pathway networks and ultimately exerts its transcriptional effects by binding to DNA sequences termed ‘androgen response elements’ that are associated with androgen-regulated genes.11 Androgenic stimulation through AR induces cell proliferation in the male reproductive system and is implicated in the development and progression of prostate cancer,10 bladder cancer,9 and a subtype of breast cancer.5 Therefore, the poorly developed GL cell nests in the castrated male hamsters may have been caused by a lack of androgen–AR signaling.

Discussion

In intact male hamsters, the nests of GL cells developed widely throughout the thoracoabdominal ventral skin and often expanded into the dorsal skin. In comparison, GL cells were less prevalent in the thoracoabdominal ventral skin and were completely absent from the dorsal skin of gonadectomized male and female hamsters and intact females. These current results coincide with the distribution of the GL cells described previously.1 In addition, the pattern of the frequent atypical skin fibromas in this species corresponds highly with the distribution of GL cells.1 Moreover, these tumor cells express AR and are morphologically similar to GL cells.1 These features suggest that these tumors may derive from GL cells. In addition to the marked sex-associated difference in GL cell distribution, the PCNA index of the GL cells and thus their proliferative capacity was higher in the intact male hamsters than in the intact females. A similar trend in the PCNA index of GL cells has been reported previously.7

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The PCNA index of the GL cells in ovariectomized female hamsters was decreased compared with that in intact females, although neither their number nor distribution differed between these groups. Ovariectomy is known to significantly decrease the androgen concentration in postmenopausal women.26 Similarly, the ovary in Djungarian hamsters may influence their serum testosterone level. The fact that the proliferative activity of GL cells was decreased in gonadectomized animals of both sexes compared with their intact counterparts could be explained by low serum levels of androgen due to gonadectomy.
The physiologic significance of GL cells remains unknown. The Harderian glands of Syrian hamsters and the abdominal scent glands in gerbils are thought to be sexually dimorphic and to produce a pheromone associated with interindividual communication. However, unlike those glandular cells, GL cells are mesenchymal cells, and it is unlikely that they produce pheromones. The role of the GL cells in male Djungarian hamsters may be quite unique.

In conclusion, the GL cells of Djungarian hamsters have clear sex-associated differences in their distribution and proliferative activity, both of which were limited by gonadectomy. In addition to their previously described AR expression, the development of GL cells likely is influenced by androgens such as testosterone.

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References
Androgen-dependent behavior of skin ganglion cell-like cells


