Development of tubular ductal complexes in exocrine pancreas acinar cells of rats in azaserine-rat model

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The tubular ductal complexes consist of duct-like structures that have seen a low incidence and smaller number in the pancreas of azaserine-treated rats. These lesions are found more characteristically in carcinogen-treated hamsters or rats treated with different carcinogens. There is little known about histologic patterns of these lesions of azaserine/rat model. Since the dominant lesions in the pancreas of azaserine-treated rats appear to be derived from acinar cells, in the present study the presence of ductal complexes provides support for the view that such lesions result from the effect of azaserine and oleic acid on acinar cell rather than on ductal cells. The tubular ductal complexes occurrence appear to effect of oleic acid feeding, but no clear evidence. The significance of these finding remains unclear. [Journal of Turgut Özal Medical Center 2(2):126-129,1995]

***Key Words** : Rat, azaserine, ductular complex, pancreas*

Azaserine-sıçan modelinde sıçanların (rat) ekzokrin pankreas asinar hücrelerde tübüler kompleks oluşumu

Azaserine enjekte edilmiş sıçanlarda (rat) tübüler kanal kompleksinin (tubular complex), kanals yapılardan meydana gelime oranı oldukça düşük olup, bu sıçanların ekzokrin pankreaslarında az sayıda bulunurlar. Bununla beraber, değişik kanserojen maddelerle enjekte edilmiş hamsterlerde bu kanals yapıların daha sık görüldükleri bilinmektedir. Azaserine enjekte edilmiş sıçanlarda tübüler kanal komplekslerinin histolojik özellikleri iyi bilinmemektedir ve azaserine enjekte edilmiş sıçanlarda ekzokrin pankreas lezyonlarının çoğunluğu hamsterlerin aksine asinar hücrelerden meydana gelir. Bu çalışmada, azaserine enjekte edilmiş ve oleik asit ile beslenmiş sıçanların ekzokrin pankreaslarında tübüler kanal komplekslerinin arttığı gösterilmiş olup bu bulguların pankreas kanserinin orijini bakımından önemi bilinmemektedir. [Turgut Özal Tıp Merkezi Dergisi 2(2):126-129,1995]

***Anahtar Kelimeler** : Sıçan, azaserine, kanals (ductal) kompleks, pankreas*

Epidemiologic studies indicate a high increase in the incidence of pancreatic carcinoma the past four decades in several countries. The reasons for this rising incidence are not clear. A number of different chemical substances are capable of inducing the neoplastic transformation of ductal and acinar cells of exocrine pancreas in experimental animals[1-3]. The histogenesis of ductal adenocarcinoma is complex and appear to involve modulation and perhaps dedifferentiation of acinar epithelial cells in addition neoplastic transformation of preexisting ductular cells. All tumours that have been induced in rat pancreas by these structurally unrelated carcinogens appear to be derived from acinar cells. The reasons for the increased susceptibility of rat exocrine pancreatic acinar cells and neoplastic transformation remain to solve. Experimental studies shown that both acinar and ductular epithelium of exocrine pancreas are capable of inducing adenocarcinoma.

Ultrastructural studies have shown that small numbers of zymogen granules persist in the cytoplasm of cells within tubular ductal complexes[4]. Tubular complexes first described in a (7,12-dimethylbenz [*a*] anthracene) DMBA-induced model of pancreatic neoplasia[3], they appear to represent a step in the development of ductular carcinogenesis[4]. These lesions are seen very rarely in azaserine-initiated rats[5]. The major objective of this paper is to

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briefly discuss the histologic property and histogenesis of a ductular complexes that increased in azaserine treated rats after %20 oleic acid feeding.

MATERIAL & METHODS

Animals and Diets

Male inbred Winstar strain rats were obtained from our breeding colony and were housed and kept five animals to a cage under standard conditions (room temperature 23 C; lighting 7am-7pm), on sawdust bedding. Standard diet (Paterson and Christopher Hill Group, Porton-Rat diet PRD) and tap water were supplied *ad libitum*.

Treatment

Starting at two weeks of age, 20 male rats received a single weekly *i.p.* (30 mg/kg body weight) dose of azaserine (Sigma Chemicals) for 3 weeks, dissolved in 0.9% NaCl solution to a final concentration of 3 mg/ml. on the day of injection. The pups were then returned to their respective dams and allowed to continue suckling until 21 days of age. On the day 21 of life, 10 azaserine-initiated rats were switched onto a normal standard diet (AzCt), 10 azaserine-initiated rats were switched onto a %20 oleic acid diet (AzOl) for 12 months, the composition of diets reported previously[6].

Histology

At the end of 12 months the rats were sacrificed by decapitation. The entire rat pancreas was excised at autopsy and all adherent fat, mesentery and lymph nodes were carefully trimmed off and fixated in 10% buffered neutral formalin for approximately 8-18 h. Sections were then cut at 5μm on a microtome and stained with haematoxylin and eosin and were examined by light microscopy. Tubular complexes in the sections were identified according to the established criteria[4,5], Only a few tubular complexes have been identified at 12 months after initial treatment with azaserine.

RESULTS

Ductular complexes

During histologic examination of pancreatic sections we came cross with a few duct-like structures in the azaserine treated (AzCt) and azaserine initiated-oleic acid fed (AzOl) rats (Figure 1). The acinar tissue of these lesions has been characterized with a lumina that are lined by a cuboidal or low columnar epithelium were associated with a scanty fibrous stroma lacking any evidence of zymogen granules (Figures 2, 3). The cells in these tubular complexes were possible degenerative acinar cells which luminal spaces were widened significantly, while the acinar cells decreased in height. These duct-like complexes exhibited strongly eosinophilic cytoplasm in the cells and this associated with in advanced level of luminal enlargement (Figure 2). The lumina contained some sort of eosinophilic material (Figure 3) but surrounding acinar cells remained normal in appearance. It has been observed that these tubular ductal complexes were tend to be found close area to acinar cell adenomas (Figure 4).

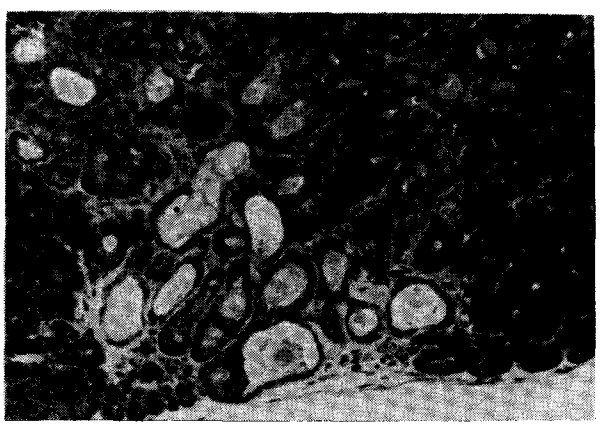

Figure 1. Photomicrograph of azaserine-treated pancreas showing replacement of acini by duct-like structure. *Haematoxylin & Eosin X* 180.

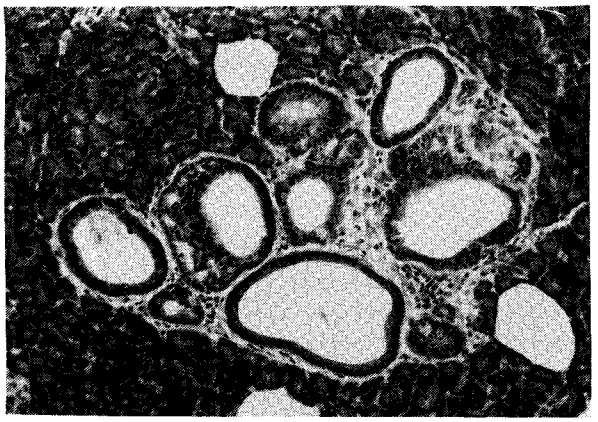

Figure 2. Tubular ductal complex, showing large nuclei and increased basophilia in the basal cytoplasm. *Haematoxylin & Eosin X 170.*

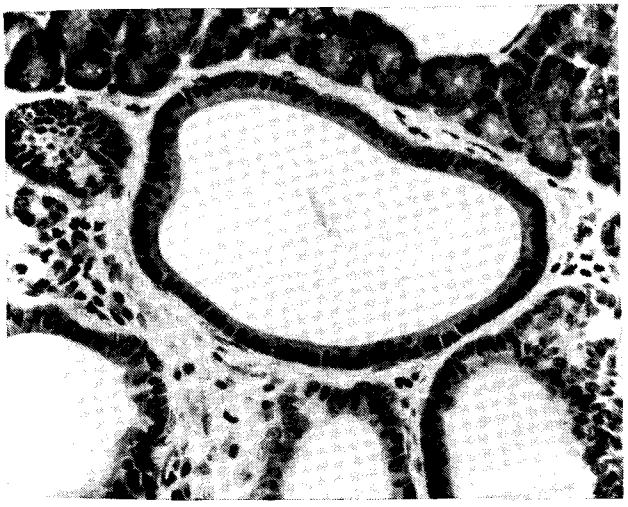

Figure 3. Detail from upper photomicrograph, tubular complex showing cuboidal and columnar epithelium. *Haematoxylin & Eosin X 270.*

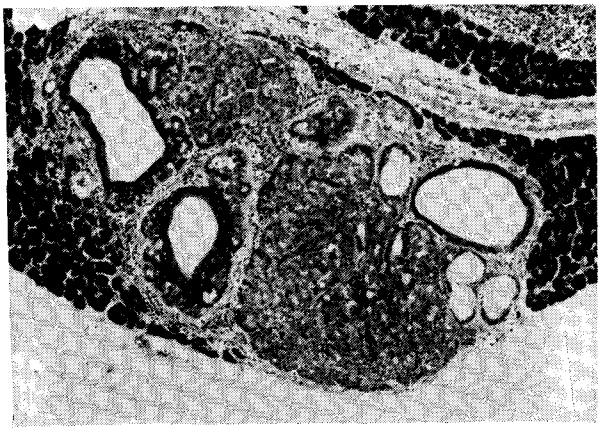

Figure 4. Acinar cell adenomas (arrow) and tubular complexes (*). *Haematoxylin & Eosin X 60.*

DISCUSSION

The histological appearance of the ductular complexes in this study were found to be in general agreement with previous reports that the origin of these lesions appears to be from acinar cells[7,8]. It has been speculated that the tubular lesions may have a capacity to grow to a large size and to progress to carcinoma[5]. Embryological studies suggest that pancreatic acini differentiate from the ductal system which appears early in the development of organ. However, the acinar cell changes have been described by various investigator in a variety of rodent species suggests that modulation of acinar cells into ductular ones is a general way[2,9,10]. On the other hand, in the hamsters treated with potent pancreatic carcinogens preexisting peri- and intralobular ducts proliferate and serve as predominant sites of adenocarcinoma formation[11]. It is probably that ductular transformation of acinar cells and preexisting peri- and intrainsular ductules may be operative in the histogenesis of chemically induced ductal adenocarcinomas of pancreas in hamster. Carcinomas of acinar cell origin have been induced in the rat and their histogenesis appears reasonable

straightforward[10]. Alteration or loss of these differentiative characteristics in acinar cells support previous findings[4,7] that acinar cells, by de-differentiating, may give rise tubular complexes. Bockman and his co-workers[8] showed that acini are not tagged to the duct system like grapes to stem, but rather are arranged in branching and anastomosing tubules with various diameters. This arrangement of the normal pancreas suggests that under pathologic conditions a decrease in acinar cell height and an increase in acinar lumen diameter could induce the formation of duct-like structures or so-called tubular complexes. In the normal pancreas pathologic conditions that can decrease acinar cell height and increase acinar lumen diameter could induce the formation of duct-like structures or tubular complexes. It has been shown that intraductal injection of oleic acid (50 microlitre) in rats can induce ductular complexes and these persist for several weeks[12]. Some of the exocrine pancreas is replaced by ductular complexes and adipose tissue about 6-7 weeks after oleic acid application. Willemer[13] speculated that the formation of tubular complexes is a general reaction of acinar cells to a variety of injuries. In the present study, ductular complexes occurrence appear to effect of oleic acid feeding, but no clear evidence. The significance of these finding remains unclear. However, investigations with various carcinogens on the rat pancreas have shown that progressive de-differentiation of acinar cells is involved in the pancreatic carcinogenesis[4,9], although Longnecker & Curphy[2] indicated that acinar cells need not lose their differentiative character totally in order to express neoplastic potential.

Ductal complexes comprise a heterogenous group that were found often in the present study. Previous work has shown that there is a connection between intraduodenal oleic acid injection and ductular complexes occurrence in rat exocrine pancreas. This study showed that oleic acid may also induce ductular complexes by oral feeding.

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