Chapter 17
What are the efferent ductules?

Rex A. Hess

Are efferent ductules part of the testis?

Efferent ductules are the numerous small, thin-walled, highly convoluted tubules that connect rete testis with the single tubule called the epididymis. Historically the efferent ducts have received far less attention than the epididymis in the male reproductive tract. However, sperm produced in copious amounts must exit the testis in a dilute physiological fluid and be transported into the epididymis for maturation, storage and then ejaculation. It is essential that transport from the testis be rapid and without obstruction, otherwise fluid will back up into the rete testis and seminiferous tubules, producing a cascade of male reproductive problems, including infertility. This important passage is dependent on the rete testis that forms chambers within the mediastinum of the testis, in man, and the series of small tubules called the efferent ductules (or ducts). The rete testis network of channels or chambers join with individual efferent ductules at the testicular surface or the tunica albuginea. The rete epithelium changes dramatically from a flattened, variable height structure to a low columnar epithelium in efferent ducts. The efferent ducts are not part of the testis, anatomically, as they reside outside the fibrous tissue capsule that covers the testis and are derived embryologically from the mesonephros. However, the answer regarding efferent ducts and the epididymis is less straightforward.

Are efferent ductules part of the epididymis?

Efferent ducts are derived embryologically separate from the rete testis, first forming as mesonephric tubules that grow out from the Wolffian duct towards the rete testis cords. Thus, it might be assumed that efferent ducts are also separate and distinct from the epididymis, which is specifically a Wolffian duct-derived tube. The problem of classification arises for two reasons: a) In man, numerous mesonephric tubules that eventually become the efferent ducts occupy the entire head of the epididymis, the region closest to the testicular hilum, with most of the efferent ducts opening individually into the proximal region of the epididymis (Fig. 1); b) In rodents, the cranial mesonephric tubules grow out from the Wolffian duct and connect individually with the rete testis cells, but new research has revealed that before birth the folded, cranial portion of the Wolffian duct becomes the "common efferent duct" into which all the efferent ductules open. In adult rodents, the common efferent duct is enclosed by the caput epididymal connective tissue capsule and empties into the initial segment of the epididymis (Fig. 1). Thus, it can be argued that at least a portion of the efferent ductules, the common duct, is embryologically related to the epididymis, at least in rodents. In man, the entire proximal (caput) epididymis (gross anatomically speaking) is occupied by the efferent ductules. Therefore, yes, the efferent ducts should be classified as a subsection of the caput epididymis. In man, this would include the entire proximal caput epididymis and in rodents this portion could be further subdivided into proximal efferent ducts, a conus region and the common duct. Early literature has at times made this association, with statements such as, "Efferent ducts of the human epididymis..." Even in the rat, early work included efferent ducts as part of the overall classification of the term "epididymis".

Structure and function of efferent ductules

Although it is reasonable to label efferent ducts as a subsection of the caput epididymis, their epithelial morphology and general physiology set them apart distinctly from the main body of the epididymis. This feature alone does not prevent the ductules from being classified as part of the epididymis, because epithelial morphology even of the epididymis in some species varies dramatically from caput to cauda. There is an abrupt epithelial change from rete testis to efferent ductules and from efferent ducts to the epididymis tubule. Rete testis epithelium is squamous to low columnar in height, with few microvilli and a single primary cilium (non-motile), while the efferent duct epithelium is abruptly taller, columnar in shape and lined by two cell types, ciliated (motile cilia) and non-ciliated with numerous short microvilli and also a primary cilium (Fig. 2). The epididymal epithelium is also recognized by its abrupt change into a tall, pseudostratified columnar epithelium, with long, branched microvilli, but no motile cilia. However, there is considerable variation in cell morphology along the length of the ductules, with

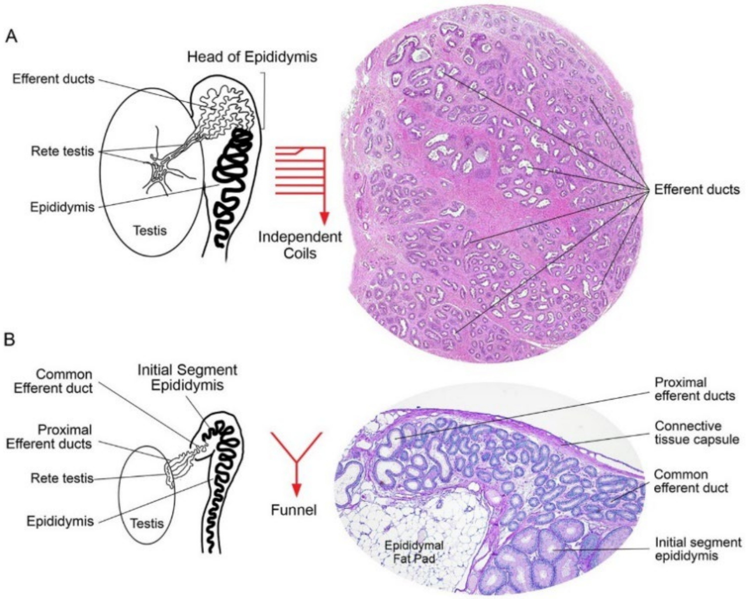

Figure 1. Two basic types of efferent ductule organization are illustrated. **(A)** "Independent coils" are found in man and larger mammals. The individual efferent ducts extend from the rete testis and most stay separated, with only a few ducts merging before opening into the epididymis. The numerous efferent ducts (approximately 15) occupy the entire proximal or head of the epididymis. Thus, there are numerous separate entries of the efferent duct lumens into the caput epididymis. Histology of the epididymal head region in man is shown on the right, with cross sections of the coiled separate ductules surrounded by thick areas of connective tissue (photo provided by Dr. Robert Sullivan, CHU de Quebec-Université Laval Research Center, Québec, QC, Canada). There is considerable variation in the luminal diameters. **(B)** The "Funnel" formation is present in rodents and smaller mammals. Individual efferent ductules (2-8) carry sperm from the rete testis, but all merge to eventually form a single, common duct that enters the head of the epididymis and opens into the initial segment. Thus, the seminiferous tubular fluid that is not reabsorbed by the efferent duct epithelium is funneled into a small, single tubule. Histology of the mouse efferent ductules is shown on the right. The proximal ducts, nearest the rete testis, have a wider lumen than those in the conus (area of merging) and common duct regions. The common duct resides under the connective tissue capsule that encloses the epididymis and opens into the larger initial segment.

species variations. The major function of efferent ducts is the reabsorption of nearly 90% of the luminal fluid, which increases the concentration of sperm as they enter the initial region of the epididymis. This function is reflected in the two epithelial cell types. Nonciliated cells have an absorptive microvillus border with endocytotic vesicles and lysosomal granules, while the ciliated cells support long motile cilia that agitate or stir the luminal fluids, which ensures the lumen does not become clogged as the sperm become more concentrated.

In man, sperm are transported through the epididymis in 1-5 days, but transit in the efferent ducts occurs within hours and even less than 1 hour in the rat. Therefore, the structure and function of these ductules must be highly regulated and well organized to avoid sperm stasis and occlusions. The ducts are organized into two basic designs (Fig. 1). In man and other larger mammals, the ductules

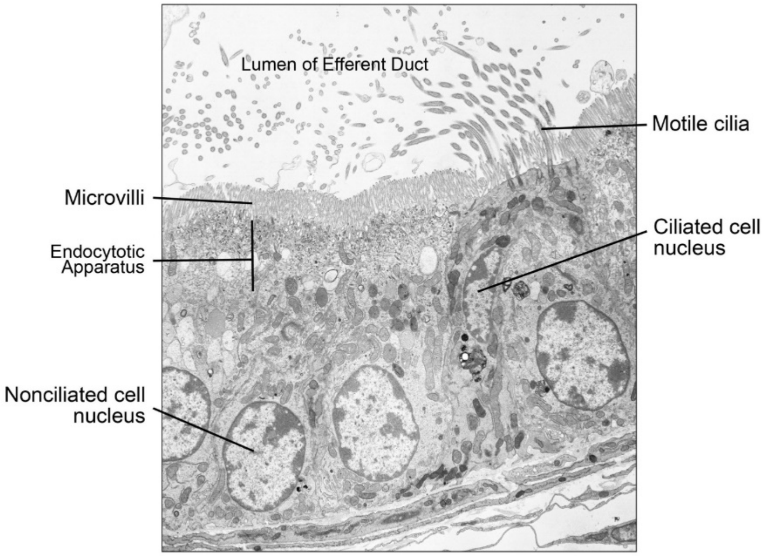

Figure 2. Efferent ductule epithelium consists of two cell types. Shown is a transmission electron microscopy section from the mouse, which is typical for all species. The nonciliated cell is lined by a short microvillus border at the lumen, which is highly absorptive as demonstrated by a prominent endocytotic apparatus. The ciliated cell supports long motile cilia that extend from basal bodies into the lumen for the purpose of stirring or agitating the luminal fluids.

form "*independent*" convolutions that occupy most of the proximal or caput epididymidis. This arrangement consists of approximately 15 adjacent strands of coiled efferent ducts extending from the rete testis, with most of these ductules remaining independent, rather than merging, and thus providing multiple entries into the initial region of the epididymis. The other basic formation is that of a "*funnel*", which is found in smaller mammalian species, including rodents. Efferent ducts with the funnel organization open separately from the rete testis (2-8 proximal ducts) but all of the ducts then begin to merge until they form a single, very thin diameter, common ductule that penetrates the epididymal connective tissue capsule for emptying into the initial segment epididymis. Thus, rapid reabsorption of luminal fluid is required to prevent overloading the volume capacity of the common duct, because all of the un-reabsorbed seminiferous tubular fluid is funneled along with the sperm into this small, single ductule. This difference in efferent ductule organization is rather significant and highly relevant to reproductive pathology in both man and other species.

Regulation and potential pathology

Androgens and the androgen receptor (AR) pathway are well known for their regulation of development and adult function of the epididymis. However, surprisingly the efferent duct epithelium is dependent on the estrogen receptor-1 (ESR1) pathway, as well as AR, for both development and function, particularly the ability to reabsorb nearly 90% of the luminal fluid. How might this discovery impact our interpretation of human epididymal pathology? Lesions are more commonly found in the caput region of the epididymis, along with the formation of sperm granulomas, which experimentally are related to disruptions in fluid reabsorption, as well as loss of ESR1 activity. A potential problem arises because most research is performed in rodent species, which carry the "funnel" organization, and thus the efferent ducts are more susceptible to total blockage. Complete occlusion of the common duct will result in azoospermia and back-pressure atrophy of the testis, a commonly reported pathology in rodent models. In man, the ductules do not funnel into a single duct and therefore, although sperm stasis and granulomas can form, there is less likelihood of total blockage and testicular atrophy. This difference between smaller and larger species raises numerous questions and requires careful extrapolation of rodent studies to man. Finally, further investigation is warranted into the potential effects on epididymal sperm and fertilizing ability in cases of partial disruption or blockage of some but not all efferent ductules.

Suggested reading

Hess RA. The efferent ductules: structure and functions. In: Robaire B, Hinton B, editors. The Epididymis: from Molecules to Clinical Practice. Kluwer Academic/Plenum Publishers, New York, NY: 2002; 49-80.

Hess RA. Efferent ductules: Structure and function. In: Skinner MK, editor. Encyclopedia of Reproduction, 2nd Ed. Oxford: Academic Press;, 2018; 1: 270-278.

Hess RA, Sharpe RM, Hinton BT. Estrogens and development of the rete testis, efferent ductules, epididymis and vas deferens. Differentiation. 2021;118:41-71.

Ilio KY, Hess RA. Structure and function of the ductuli efferentes: a review. Microsc Res Tech. 1994;29(6):432-67.

Legare C, Sullivan R. Differential gene expression profiles of human efferent ducts and proximal epididymis. Andrology. 2020;8(3): 625-36.

Omotehara T, Nakata H, Nagahori K, Itoh M. Comparative anatomy on the development of sperm transporting pathway between the testis and mesonephros. Histochem Cell Biol. 2022;157(3):321-32.

Saitoh K, Terada T, Hatakeyama S. A morphological study of the efferent ducts of the human epididymis. Int J Androl. 1990;13(5):369-76.

Sullivan R, Legare C, Lamontagne-Proulx J, Breton S, Soulet D. Revisiting structure/functions of the human epididymis. Andrology. 2019;7(5):748-57.

Yeung CH, Cooper TG, Bergmann M, Schulze H. Organization of tubules in the human caput epididymidis and the ultrastructure of their epithelia. Am J Anat. 1991;191(3):261-79.

Yuan S, Liu Y, Peng H, Tang C, Hennig GW, Wang Z, Wang L, Yu T, Klukovich R, Zhang Y, Zheng H, Xu C, Wu J, Hess RA, Yan W. Motile cilia of the male reproductive system require miR-34/miR-449 for development and function to generate luminal turbulence. Proc Natl Acad Sci U S A. 2019;116(9):3584-93.