



Current opinion

## Is the metrial gland really a gland?

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An intriguing history surrounds the ‘metrial gland’. It is a term coined by Selye and McKeown (1935) to describe a pregnancy-specific modification of the mesometrial uterus juxtaposed to the developing chorioallantoic placenta of the rat. Selye and McKeown were justifiably fascinated with the prominent secretory granules present within cells of the structure and were aware of the earlier speculations about the endocrine activity of the tissue (Ancel and Bouin, 1911; Weill, 1919; Gerard, 1927). The term, ‘metrial gland’, has been used to describe similar anatomical regions in other species, including the mouse. Experimental approaches employed to study the ‘metrial gland’ have generally had some bias. The metrial gland has been viewed as a panacea for the adventurous endocrinologist, immunologist, and reproductive biologist. In recent years, there has been considerable discussion about the suitability of the term ‘metrial gland’ (Croy, 1999; Stewart, 1999, 2001; Pijnenborg, 2000).

In her provocative commentary Croy questioned the use of the term ‘metrial gland’ to describe the uterine mesometrial compartment (Croy, 1999). She stated: “The ‘metrial gland’ is not epithelial in origin, is dissimilar in histological structure to other glands and has not been found to have endocrine or exocrine functions.” We take exception with this assessment, as is addressed below. Croy further recommended the use of the term ‘mesometrial lymphoid aggregate of pregnancy’ instead of ‘metrial gland’. Pijnenborg and Stewart concurred with the limitations of the term ‘metrial gland’. They aptly discussed aspects of the complex cellular composition of the structure, its dynamic nature, and its species-specific characteristics; and likewise offered their own preferred terminology (Stewart, 1999, 2001; Pijnenborg, 2000).

We have been drawn to the ‘metrial gland’ of the rat from yet a different vantage point. A population of cells within the ‘metrial gland’ is a target of prolactin (PRL)-like protein-A (PLP-A). PLP-A is a member of the PRL family of hormones/cytokines produced by trophoblast cells (Soares and Linzer, 2001). PLP-A is present in maternal circulation and

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specifically targets and influences the activity of natural killer cells that reside in the ‘metrial gland’ at midgestation (Deb and Soares, 1990; Müller et al., 1999; Ain et al., 2003b). Most recently we have discovered that PLP-A and three other members of the PRL family (PLP-L, PLP-M, and PLP-N) are produced in the ‘metrial gland’ (Ain et al., 2003a; Wiemers et al., 2003b). PLP-N is part of a trophoblast-hepatic signaling axis and specifically binds to hepatocytes (S. Ohboshi and M.J. Soares, unpublished results). Targets for PLP-L and PLP-M have not been determined. Trophoblast cells are the sites of synthesis of the PRL family hormones within the ‘metrial gland’. These cells are epithelial as indicated by their expression of cytokeratins. During the last week of gestation, trophoblast cells exit the chorioallantoic placenta and invade into the ‘metrial gland’ where they assume a prominent endocrine role (Bridgman, 1949; Pijnenborg et al., 1981; Ain et al., 2003a; Wiemers et al., 2003b). Within the ‘metrial gland’, they are situated in endovascular, perivascular, and interstitial locations. Trophoblast cell entry into the ‘metrial gland’ is precisely timed and coincides with the disappearance of natural killer cells from the ‘metrial gland’ (Ain et al., 2003a). The life span of trophoblast cells residing in the ‘metrial gland’ extends until after parturition (R. Ain and M.J. Soares, unpublished results). Invasive trophoblast cells of the mouse show similar endocrine activities and timing to those of the rat but are more restricted in terms of the depth of their penetration into the uterine mesometrial compartment (Redline and Lu, 1989; Teesalu et al., 1998; Ain et al., 2003a; Wiemers et al., 2003a). Mouse invasive trophoblast cells are generally confined to the decidua basalis and do not extend into the ‘metrial gland’.

We conclude that the term ‘metrial gland’ is an appropriate descriptor for the uterine mesometrial compartment of the late gestation rat. Selye and McKeown’s (1935) term was correct and the ‘metrial gland’ can be considered a gland. The limitations of the moniker are that it is not a valid term for earlier stages of rat gestation nor is it necessarily appropriate for other species. There are two key points related to the ‘metrial gland’ that should be emphasized: (1) a common theme is that the ‘metrial’ is the uterine entry point of blood vessels supplying each placenta and fetus and thus its biology and pathology should be of considerable interest to investigators studying mechanisms underlying diseases, such as preeclampsia and intrauterine growth restriction; (2) the cellular composition of the ‘metrial gland’ is dynamic and has elements of species-specificity. In the rat, natural killer cells and trophoblast cells likely each function in a gestation-dependent mode to orchestrate uterine spiral artery remodeling, facilitating blood flow to the placentas and fetuses.

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