Letter

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# Pre-Paget cells express a Paget cell marker before losing a keratinocyte marker

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**SUMMARY** Extramammary Paget's disease (EMPD) is a cancer of the anogenital epithelium. Its origin has been variously attributed to keratinocytes or to Toker cells. Slides of 3 advanced cases of EMPD were incubated with trypsin to retrieve antigens. The slides were then stained with rabbit polyclonal anti-carcinoembryonic antigen to mark Paget cells and mouse monoclonal anti-cytokeratin 10 to mark keratinocytes. Several cells in each case stained with both the Paget cell marker and the keratinocyte marker. The presence of cells with both markers shows that Paget cells originate from keratinocytes. The presence of pre-Paget cells in advanced cases of EMPD shows that Paget cells are continuously recruited from keratinocytes.

***Keywords*** extramammary Paget's disease, EMPD, carcinoembryonic antigen, cytokeratin 10

Extramammary Paget's disease (EMPD) is a cancer that arises in the epidermis of the anogenital region and expands and migrates in the epidermis before invading the dermis (*1*). Its incidence has increased during the last generation (*2*).

Toker cells, which resemble Paget cells, have been suggested as the source of EMPD (*3*), but they are not seen in most cases of EMPD (*4*). There have been several observations of a few cells with the morphology of keratinocytes that do express a Paget cell marker in cases of EMPD (*5,6*). None of these observations provided histochemical evidence that the rare cells with Paget cell markers were keratinocytes.

Cytokeratin 10 (CK10) is a keratinocyte marker which has not been observed in Paget cells (*7*). Carcinoembryonic antigen (CEA), recently renamed CD66e, is a Paget cell marker which is never expressed in normal epidermis (*8*).

Mounted formalin-fixed paraffin-embedded sections of 3 cases of EMPD, 2 in the labium majus and 1 in the hood of the clitoris, were obtained from the Cooperative Human Tissue Network. Antigens were retrieved by exposure to 0.05% trypsin for 20 min at 37oC. Nonspecific antibodies were blocked by 30 min incubation in 2.5% normal horse serum. The tissue was incubated overnight in a 1:1 mixture of 1/20 mouse monoclonal anti-CK10 (Genetex GTX21421) and 1/100 rabbit polyclonal anti-CD66e (GTX108732) in PBS. The tissue was stained with Duett conjugated secondary antibody mixture (Vector Labs MP-7724), DAB, and Vector Red.

There were many areas of confluent Paget cells, but there were also areas of morphologically normal keratinocytes. All keratinocytes expressed CK10. Almost all Paget cells expressed carcinoembryonic antigen. A few morphologically normal keratinocytes expressed both CK10 and CEA (Figure 1 and Figure 2). These cells are so few in number that they are easily missed (Figure 1). Rarely, cells expressing both CK10 and CEA were too close to round for normal keratinocytes (Figure 3).

The presence of cells expressing both CK10 and CEA in these cases proves that at least some cases of EMPD originate from keratinocytes. Cells expressing both markers must be pre-Paget cells. This conclusion is reinforced by the presence of rare cells expressing both markers that are intermediate in shape between keratinocytes and Paget cells (Figure 3).

The presence of pre-Paget cells in advanced cases of EMPD shows that malignant changes occur repeatedly in EMPD rather than in just a single progenitor cell. This can lead to multfocal extramammary Paget's disease (*1,9*).

While the expression of carcinoembryonic antigen may not be the first step in the malignant transformation of a keratinocyte in EMPD, it seems to be an essential step (*10*). The fact that most cells expressing both CK10 and CEA have the morphology of keratinocytes suggests that the expression of CEA is an early step. The expression of carcinoembryonic antigen probably

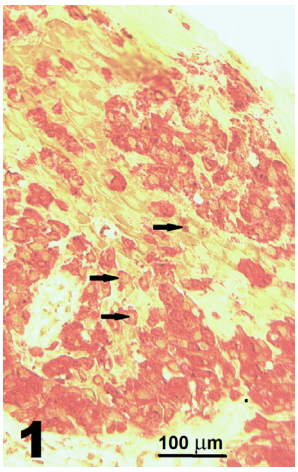


**Figure 1. EMPD of the labium majus.** Two pre-Paget cells (solid arrows) are present in the lower epidermis. Cytokeratin 10 (CK 10) stained with diaminobenzidine (DAB); carcinoembryonic antigen (CEA) stained with Vector Red.

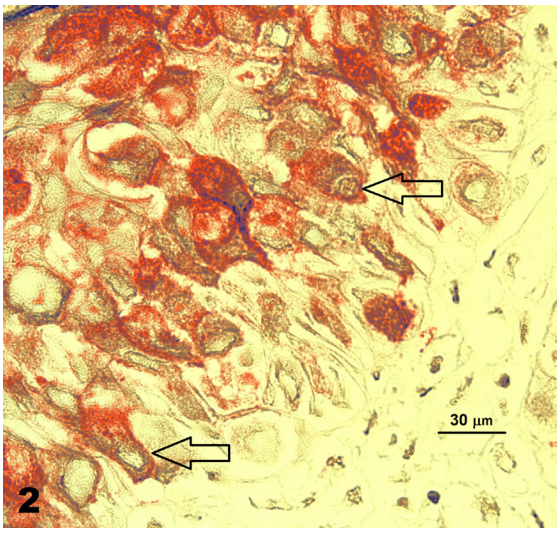


**Figure 2. EMPD of the clitoridal hood.** One pre-Paget cell is in the basal epidermis; a second is in the stratum spinosum (hollow arrows). CK10 stained with DAB; CEA stained with Vector Red.

blocks differentiation of keratinocytes just as it blocks differentiation of myoblasts (*10*).

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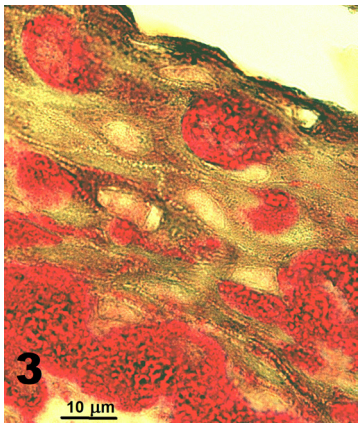


**Figure 3. EMPD of the labium majus.** A pre-Paget cell in the upper epidermis has almost completed its transition to a Paget cell. CK10 stained with DAB; CEA stained with Vector Red.

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