ONCOLOGY

Emergence and Development of Dysplasia of the Uterine Cervical Epithelium

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 129, No. 3, pp. 329-332, March, 2000
Original article submitted June 24, 1999

Dysplasia of the cervical uterine epithelium results from deficit in «initial» cells, which disturbs regulation of cell differentiation: maternal cells do no over daughter cells, which leads to attenuation of field interactions between these cells and inhibits differentiation of daughter cells.

Key Words: *dysplasia; differentiation; field interrelationships*

It is now accepted that the development of invasive cancer is preceded by dysplastic changes in the epithelium. Such states attract special interest due to initial disorders of cell proliferation and differentiation. A system created in normal epithelium during its functioning and regulating cell proliferation and differentiation was described [4,5]. Normal cell differentiation in the epithelium is possible if maternal cells (MC) predominate in the second form, where field interactions between maternal and daughter cells (DC) occur. The higher is the count of MC, the greater field they create and hence, the more intensely affect DC [2]. We investigated this system under conditions of dysplasia in order to detect the disorders leading to dysplasia and its progress.

MATERIALS AND METHODS

Smears-imprints of cervical epithelium from women with first-, second-, and third-degree dysplasia (15 patients per stage) and 20 controls were examined (a total of 65 samples, age of examinees 50-60 years). Ther specimens were fixed in Carnoy fluid, stained with hematoxylin and eosin, and morphometric analysis was carried out on a Kontron image analyzer. The area of cell nuclei (S), ellipticity degree (ED, ratio of the least to the greatest nucleus diameter), and the inclination of long nuclear axes to the abscissa were determined. Nucleur inclination helps evaluate cell disposition on the plane and analyze the fields formed by parallel nuclei [1,7]. MC and DC per 250 cells were counted by distribution histograms using the above parameters and the relative content of these cells was evaluated.

RESULTS

Regulation of cell differentiation is provided mainly by interactions between MC and DC derived from "initial" cells. MC and DC differ by their orientation on the plane: they are always perpendicular to each other. The MC-DC complex exists in two forms, type I and type II. Type I MC and DC are of the same size (S=61.14 μ^2, ED=0.9258) and are perpendicular to each other, while type II cells are also perpendicular, but are smaller than type I cells (S=52.41 μ^2) and elongated (ED=0.6124). Type II cells are more potent bipolar cells than type I cells [2,4], and therefore cell differentiation immediately in the system of type II cells. Among type II cells MC always predominate over DC due to replenishment with type I cells, which

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0007-4888/00/0003-281$25.00

provides field effect of MC on DC and induces differentiation of DC. Hence, the MC-DC relationship is realized on the basis of field interactions and disparity between types I and II. This disparity between MC and DC first develops at the end of the restoration and beginning of the proliferative period as follows: type I MC are transformed into type II MC and join them (thus the number of type II MC is increased). The MC:DC ratio initially equal to 1:1 for both types becomes 1.5:1 in the type II population.

In first-degree dysplasia these changes occur directly in the cell differentiation system, *i. e.*, in the types I and II MC-DC system. Like in normal epithelium, in cervical dysplasia the disparity of type II MC-DC is reached by the beginning of proliferation in the epithelium (Fig. 1). The number of type II MC cells increases due to replenishment with type I MC cells, the way it occurs in normal epithelium. However in dysplasia MC do not preponderate in type II system like it occurs normally, because the number of type I cells joining type II cells is decreased *vs.* the norm (Table 1). The number of type I cells is low because the number of initial cells, the source of their formation, drops in first-degree dysplasia (Table 1). Hence, a deficit of initial cells leads to alteration of the quantitative composition of the entire system of type I-II cells, which manifests by insufficient predominance of type II MC over DC. This attenuates the field created by MC and decreases its effect on DC. Hence, in first-degree dysplasia DC undergo differentiation weaker than normally.

Further progress of dysplasia (second and third degree) involves a still greater decrease in the number of MC and hence, changes in the MC:DC ratio (Table 1). Therefore, the field generated by MC and affecting DC will be much weaker than normally or in first-degree dysplasia, which will lead to further deterioration of cell differentiation.

There are two parallel rows of dividing cells in epithelial population: 1) "initial" cells and their earliest descendants (type I and II MC and DC), whose

TABLE 1. Characteristics of Epithelial Cell Differentiation Systems in Health and Dysplasia

Parameter	Norm	Dysplasia	
		I degree	II degree
Number of "initial" cells	0.6	0.4*	0.3*
Number of type I cells joining type II cells	0.5	0.35*	0.25*
MC:DC	1.5:1	1.4:1	1.3:1

Note. $p<0.05$ *vs.* the norm.

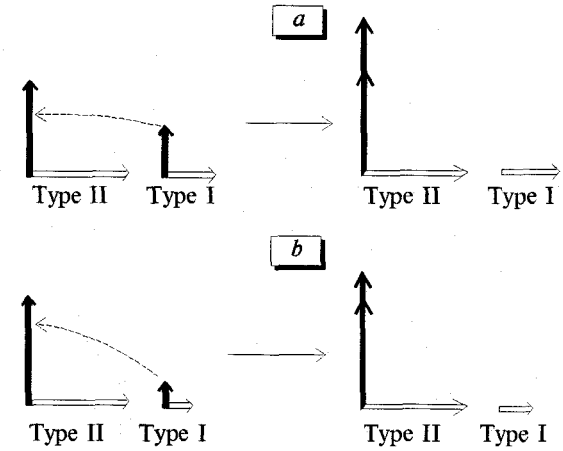

Fig. 1. Formation of predominance of maternal cells (dark arrows) over daughter cells (light arrows) in normal epithelium (*a*) and epithelium with third-degree dysplasia (*b*).

division and differentiation gives «reserve» cells and 2) reserve cells and their derivatives, which proliferate and are directly involved in physiological regeneration of epithelium [3,5].

The proliferative activity of initial cells and their derivatives in normal epithelium corresponds to those of reserve cells. In dysplasia the first-flow cells more rapidly than second-flow ones pass through stages of active proliferation and attenuation of mitotic activity, because of decreased number of initial cells. In dysplasia of the third degree a greater decrease in the number of initial cells results in a greater discrepancy between the proliferative activities of the first and second flow. Analysis of histograms of cell distribution by ED showed that first-flow cells virtually skip the period of mitotic activity attenuation and are transferred immediately into the restorative period, while second-flow cells still actively proliferate. During the restorative period in normal epithelium the numbers of types I and II MC and DC normalize and attain the level observed at rest [6]. The number of types I and II cells is restored by division of the initial cells, the number of type I cells always being half of the number of type II cells.

Two stages are distinguished in the restorative period: early and late (Fig. 2). Normally during the early period the number of type II cells increases 1.5 times at the expense of joining type I cells, constituting half of type II cells. The proportions of type II MC and DC are thus equilibrated and cell differentiation is blocked. During the late period the type II MC-DC ratio is again unequilibrated because of type I MC joining type II MC. Moreover, the number of type II cells is increased 1.3 times more, which makes almost twofold over the entire restorative period. In third-degree dysplasia the initial cells actively proliferate due to this discrepancy by the beginning of the restorative

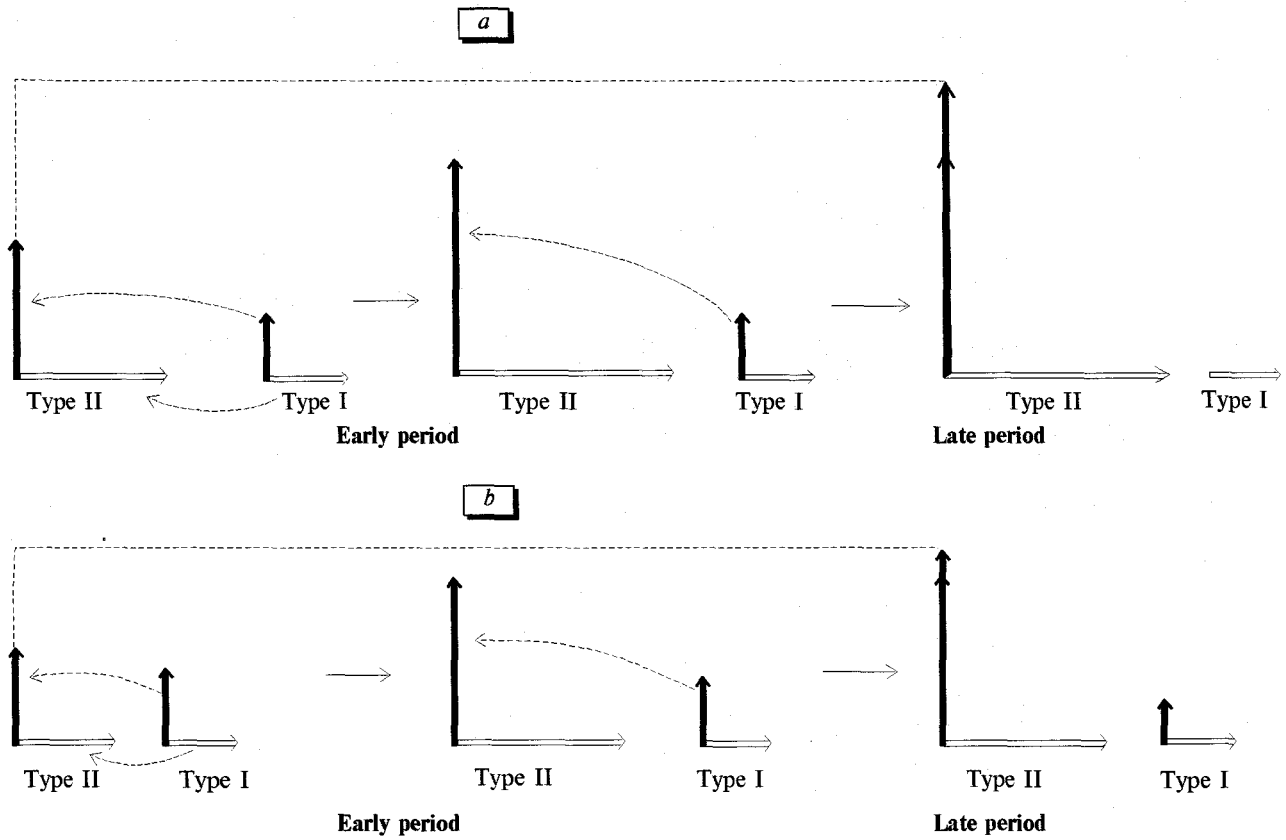

Fig. 2. Distribution of maternal (dark arrows) and daughter (light arrows) Type a I and II cells in the restorative period in normal epithelium (*a*) and epithelium with third-degree dysplasia (*b*).

period, which leads to excessive increase in the number of type I cells (0.8 instead of 0.5 in health, $p<0.05$) and approximation of this number to that of type II (1.0). As a result, the number of type II cells during the early restorative period is increased not 1.5 times, which is normal, but almost twofold, and therefore the creation of sufficient predominance of MC over DC during the late period is impossible, because the number of type II cells increased almost to the limit (twofold) during the early period. This leads to equilibration of cells within each type and between type I and type II cells. An almost equilibrated state is created inside the system.

Hence, the deficit of initial cells attenuates differentiation of DC and leads to development of dysplasia. Further decrease in their count leads to progress of dysplasia, manifesting by almost equilibrated state between type I and type II cells during the restorative period. Fields generated by cells of both types in such a ratio are almost compensated, which leads to the maximum decrease in cell differentiation.

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