Ki67 and CD44 as markers of colorectal cancer`s carcinogenesis models

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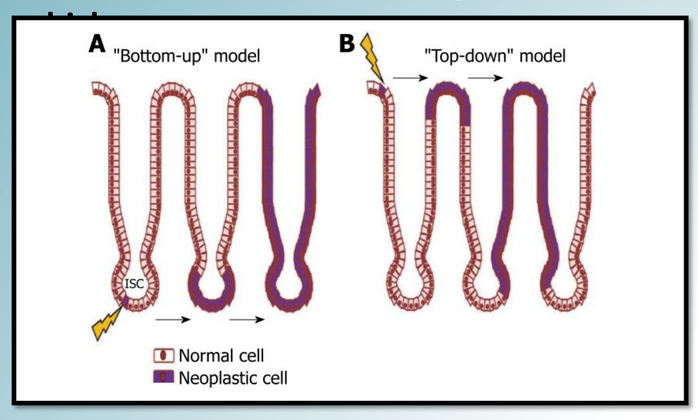
Objective

Hyperplastic polyps (HP), sessile serrated adenomas (SSA), adenomas tubular (AT), adenomas tubulo-villuos (ATV) and traditional serrated adenomas (TSA) are considered to be possible colorectal cancer's precursors. There are two colorectal cancer`s carcinogenesis models: "bottom-up" and "top-down" are declared as alternative. However there is no data about cancer's precursors and cancer`s carcinogenesis matching. CD44 is cell adhesion molecule, which is involved in many types of carcinogenesis including colon&rectum. Ki67 is protein of proliferative activity, reflecting the proliferating processes alterations in tumour.



Puglisi MA. Colon cancer stem cells: controversies and perspectives. World J Gastroenterol 2013; 19(20): 2997-3006

Methods

We assessed immunohistochemical expression of Ki67 and CD44 in 13 hyperplastic polyps (HPs), 19 sessile serrated adenomas/polyps (SSAs), 17 traditional serrated adenomas (TSAs), 18 tubular adenomas (ATs), 16 tubulovillous adenomas (ATVs). In all cases we evaluated the distribution of markers in colon crypt (bottom, middle or upper third of crypt). For statistical analysis PASW Statistics 22 was used.

Results

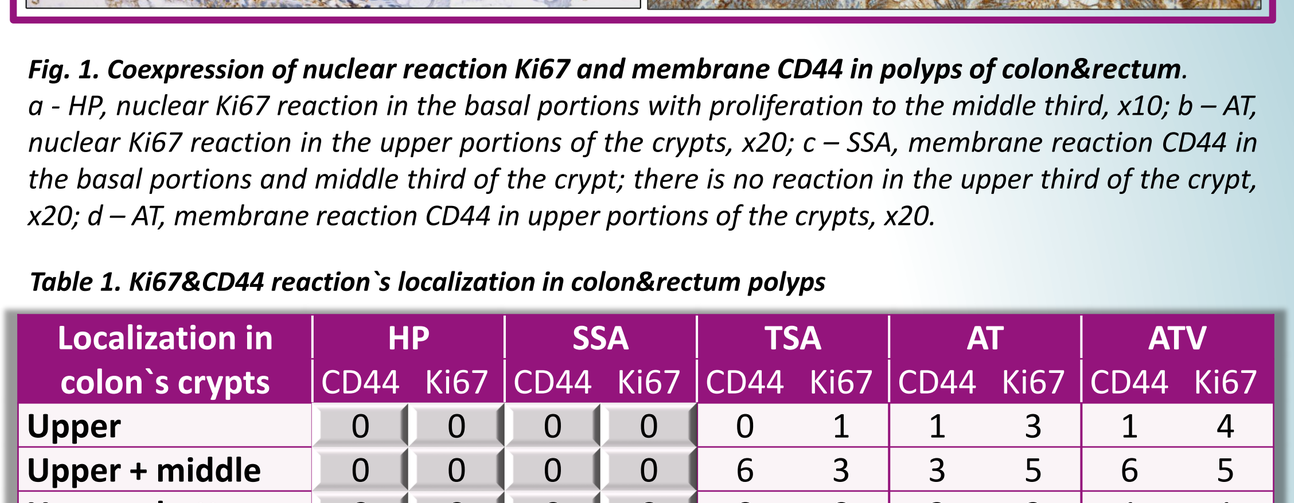
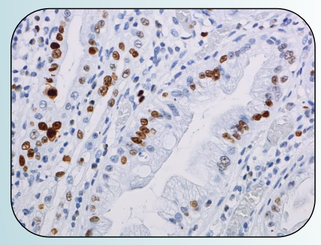
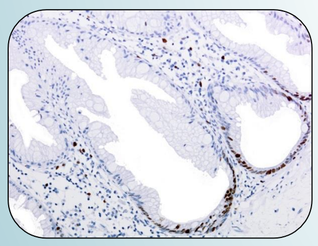


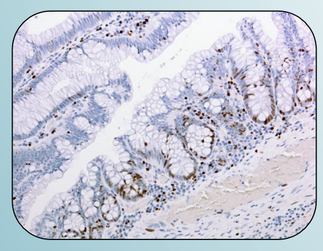
Fig. 1. Coexpression of nuclear reaction Ki67 and membrane CD44 in polyps of colon&rectum.
a - HP, nuclear Ki67 reaction in the basal portions with proliferation to the middle third, x10; b – AT, nuclear Ki67 reaction in the upper portions of the crypts, x20; c – SSA, membrane reaction CD44 in the basal portions and middle third of the crypt; there is no reaction in the upper third of the crypt, x20; d – AT, membrane reaction CD44 in upper portions of the crypts, x20.

Table 1. Ki67&CD44 reaction`s localization in colon&rectum polyps

Localization in colon`s crypts	HP		SSA		TSA		AT		ATV	
	CD44	Ki67	CD44	Ki67	CD44	Ki67	CD44	Ki67	CD44	Ki67
Upper	0	0	0	0	0	1	1	3	1	4
Upper + middle	0	0	0	0	6	3	3	5	6	5
Upper + bottom	0	0	0	0	0	0	3	3	1	1
All crypt	0	0	0	0	11	13	10	7	8	6
Bottom	5	9	17	19	0	0	0	0	0	0
Bottom + middle	7	4	2	0	0	0	0	0	0	0
Negative	1	0	0	0	0	0	1	0	0	0
TOTAL	13		19		17		18		16	







KI67

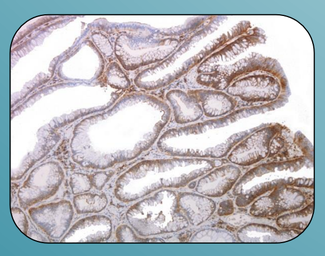
In HPs two types of mark distribution were observed:

- **reaction in the basal portions of the polyp (69,8%)**
- **reaction in the basal portions with proliferation to the middle third of the polyp (30,2%)**

In SSAs only one variant of mark distribution was observed: in the basal portions of the polyp, (in the lower third of the crypts) (100%), without proliferation to the middle third.

The nature of Ki67 reaction in TSAs, ATs and ATVs was fundamentally different. The mark distribution along the height of the crypt was different:

- **uniformly diffuse throughout the polyp;**
- **mainly in the superficial portions of the adenoma (the upper third of the crypts).**



CD44

In HP and SSA, the CD44 reaction had a membrane nature and was detected in the basal portions of the crypts (the lower third). In 23.3% of HP and only in 12.2% of SSA, the reaction was also detected in the middle portions.

In all TSAs, the CD44 reaction was observed in the upper and middle thirds. In a number of cases (65.6%), the reaction was also detected in the lower third. It is noteworthy that even if the reaction was observed diffusely throughout the adenoma (*i.e.,* in the upper, middle, and lower thirds of the crypt), a gradient was there in 52.9%: the reaction was significantly more pronounced in the apical portions of the crypts facing the lumen than in the basal ones, which indicated the proliferation of the reaction "from the top downward" for TSA, in contrast to HP and SSA.

CD44 expression was characterized by exactly the same patterns of polyp distribution, as was Ki67, although CD44 did not reflect proliferative activity. Thus, in 70.6% (12/17) TSA, 89.5% (17/19) SSA and 23.1% (3/13) HP, the localization of these markers completely coincided. Between the distribution of Ki67 and CD44, weak and moderate positive correlations were observed in all thirds of the crypt (the upper third r = 0.29, p = 0.03, the middle r = 0.31, p = 0.04, the bottom r = 0, 46, p = 0.001, for a uniform distribution of r = 0.33, p = 0.01). Such coexpression can be explained by the involvement of CD44 molecules in the transmission of specific signals through cytoskeleton components, which stimulates an increase in mitotic activity of cells.

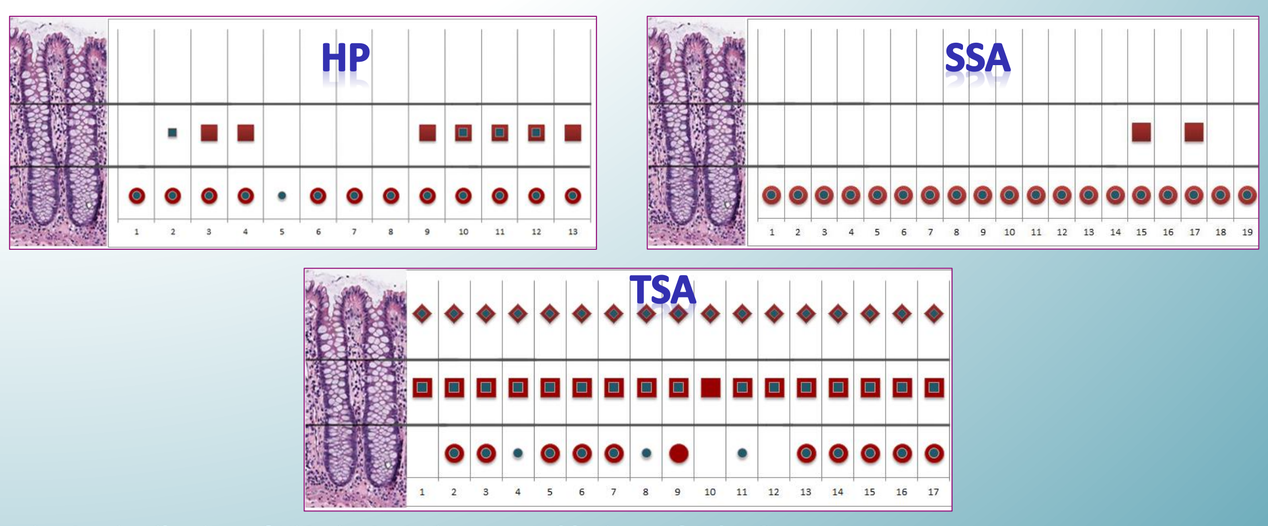


Fig. 2. Distribution of Ki67 in CD44 in serrated lesions of colon&rectum.
In each case, the red symbols indicate the presence of a CD44 reaction in the upper, middle or lower third of the crypt; green - reactions Ki67. When the locations coincide, the symbols overlap.

Conclusion

The described models of carcinogenesis are not alternative. AT, ATV and TSA are characterized by a "top-down" model, for HP and SSA, on the contrary, "bottom-up". These circumstances indicate the fundamental difference between AT&ATV from HP&SSA and emphasize the similarity of TSA and AT&ATV.

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