Colon cancer cells produce immunoregulatory glucocorticoids

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Keywords: Immune evasion, glucocorticoids, steroidogenesis, liver receptor homolog-1, colon cancer, apoptosis

Abbreviations: APC, adenomatous polyposis coli; EGF, epidermal growth factor; LRH-1, liver receptor homolog-1/NR5a2; TNFα, tumor necrosis factor α

Expression or release of immunosuppressive molecules may protect tumor cells from the recognition and destruction by the immune system. New findings indicate that colorectal tumors produce immunoregulatory glucocorticoids and thereby suppress immune cell activation. The nuclear receptor LRH-1 plays a critical role in the regulation of colorectal tumor proliferation and glucocorticoid synthesis.

Immune responses against tumors and their role in the control of tumor development are a complex and in many aspects a rather controversial issue. While there is strong evidence from a variety of experimental systems as well as clinical studies with tumor patients that immune cells and their effector functions may limit tumor growth, other data indicate that immune cell-derived factors and associated inflammation rather enhance tumor cell survival and growth. Thus, the role of anti-tumor immune responses in the control of tumor development is not yet universally solved.

Yet, if anti-tumor immune responses are indeed able to limit or suppress tumor development, the prediction can be made that immunosuppressive factors released by tumor cells will likely enhance tumor survival and growth. In line with this notion are recent tumor patient-based studies on the correlation between patient survival and tumor infiltration by immune cells, demonstrating that high levels of memory T cells are a good and positive prognostic factor for the overall patient’s survival (reviewed in ref. 1). While these data convincingly demonstrate that presence or absence of anti-tumor immune responses determines the patient’s fate, it is presently unclear how tumor cells prevent immune cell infiltration and thereby can evade host defense mechanisms.

In a recent study published in OncoImmunology, we now show that colorectal tumors are a rich source of immunoregulatory glucocorticoids and propose that tumor-derived glucocorticoids may contribute to immune evasion by inhibiting immune cell activation and promoting apoptosis. Glucocorticoids are steroid hormones with important anti-inflammatory and pro-apoptotic properties. Though the adrenal glands are the most prominent source of glucocorticoids, alternative sources have been demonstrated, including thymus, skin, intestine and the lung.9,10 Our own studies identified the proliferating cells of the intestinal crypts as the major source of intestinal glucocorticoids in response to immunological stress.1 In the intestine LRH-1 critically regulates glucocorticoid production (LRH-1, NR5a2). LRH-1 is a transcription factor liver receptor homolog-1 (LRH-1, NR5a2). LRH-1 is a transcription factor with an increasingly recognized role in metabolism, cell cycle regulation and steroid synthesis (reviewed in ref. 8). In the intestine LRH-1 critically regulates immune cell-induced glucocorticoid synthesis via the induction of steroidogenic enzymes,11 and consequently LRH-1-deficient mice are more susceptible to the development of experimental colitis.12 As in primary intestinal crypt cells, LRH-1 is also a critical regulator of glucocorticoid synthesis in colorectal tumor cells. Not surprisingly, while in primary epithelial cells...
While the induction of glucocorticoid

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tumor cells.2 Likely, LRH-1 has a dual role

is massively overexpressed in colorectal

proliferating cells of the crypts, LRH-1

cells LRH-1 expression is restricted to the

and steroidogenic enzymes (cytochrome P450 enzymes, Cyp), leading to the synthesis

of glucocorticoids (GC). Glucocorticoids in turn suppress the activation of cytotoxic T cells and

innate immune cells. LRH-1 can also be activated via the MAP kinase (MAPK) pathway upon

stimulation of growth factor receptors, such as the epidermal growth factor (EGF) receptor.

Along these lines it was shown that LRH-1 promotes adenoma development in the APC−/− mouse model for intestinal tumor formation.8

Signals leading to LRH-1 activation are thus most interesting targets for the treatment of colorectal tumors by simulta-

neously targeting proliferation and glucocorticoid synthesis. Interestingly, signaling pathways regulating the proliferation in primary and tumor cells, such as the EGF receptor signaling pathway, have also been shown to promote LRH-1 activation.9

Surprisingly, even TNFα, a cytokine well known for its pro-inflammatory and immunosuppression properties, was recently identified by us as a key regulator of intestinal glucocorticoid synthesis,9 and could thus also likely promote glucocorticoid synthesis in colorectal tumor cells (Fig. 1). Future studies specifically target-

ing the glucocorticoid synthesis in tumor cells, e.g., by LRH-1 antagonists or inhi-

bitors of steroidogenic enzymes, have to further evaluate the importance of extra-

adrenal glucocorticoid synthesis in the development of colorectal cancer.

In summary, our present study descri-

bes for the first time glucocorticoid syn-

thesis in tumor cells from non-endocrine tissue and its regulatory activities on immune cells. As we recently also identi-

fied the lung mucosa as a rich source of glucocorticoids,4 suggesting that also lung cancer cells may be able to produce glucocorticoids, it is very likely that glucocorticoid synthesis by tumor cells is a more general mechanism of immune evasion by epithelial tumors.

References

1. Pagès F, Galey J, Deen-Najjar MC, Tarré E, Samit-Fishman C, Frédieu WH. Immune infiltration in human tumors: a prognostic factor that should be in spotlight. Oncogene 2010; 29:1933-102; PMID: 20946355; http://dx.doi.org/10.1038/onc.2009.610.

2. Sidler D, Renzulli P, Schnoz C, Berger B, Schneider-

Jakob S, Flück C, et al. Colon cancer cells produce immunomodulatory glucocorticoids. Oncogene 2011; 30:2391-9; PMID:21258443; http://dx.doi.org/10.1038/onc.2010.629.

3. Noti M, Sidler D, Brunner T. Extra-adrenal gluco-
corticoid synthesis in the intestinal epithelium: more for the first time glucocorticoid synthesis. J Exp Med 2006; 203:2057-62; PMID:16923850; http://dx.doi.org/10.1084/jem.20060357.

4. Cima I, Corazza N, Mueller C, Berger B, Brunner T, TNF suppresses acute intestinal inflammation by inducing local glucocorticoid synthesis. J Exp Med 2006; 203:2057-62; PMID:20235964; http://dx.doi.org/10.1084/jem.20050648.

5. Corazza N, Magnier B, Noti M, et al. LRH-1-mediated gluco-
corticoid synthesis in enterocytes protects against inflammatory bowel disease. Proc Natl Acad Sci U S A 2007; 104:19880-1983; PMID:17970940; http://dx.doi.org/10.1073/pnas.0705821104.

6. Noti M, Corazza N, Miehle C, Berger B, Brunner T. TNF suppresses acute intestinal inflammation by inducing local glucocorticoid synthesis. J Exp Med 2006; 203:2057-62; PMID:16923850; http://dx.doi.org/10.1084/jem.20060357.

7. Cima I, Deen-Najjar MC, Tarré E, Samit-Fishman C, Frédieu WH. Immune infiltration in human tumors: a prognostic factor that should be in spotlight. Oncogene 2010; 29:1933-102; PMID: 20946355; http://dx.doi.org/10.1038/onc.2009.610.

8. Fernandez-Macson MF, Aizen J, Schweikert K. Emerging actions of the nuclear receptor LRH-1 in the gut. Inflamm Bowel Dis 2011; 17:947-55; PMID: 21914963.

9. Noti M, Cima I, Noti M, Berger B, Jakob S, Dahlsgaard S, et al. The nuclear receptor LRH-1 critically regulates extra-adrenal glucocorticoid synthesis in the intestine. J Exp Med 2006; 203:2057-62; PMID:16923850; http://dx.doi.org/10.1084/jem.20060357.

10. Lee YK, Choi YH, Chua S, Park YJ, Moser DC. Periphery of the large, a cytokine

Fig. 1

Proposed role of LRH-1 and glucocorticoid synthesis in tumor immune evasion. Tumor-infiltrating immune cells, such as T cells, macrophages (MB) and dendritic cells (DC), release factors, such as TNFα, which stimulate the activation of the transcription factor LRH-1 in colorectal tumor cells. LRH-1 regulates the transcription of cyclins, leading to tumor cell proliferation, and steroidogenic enzymes (cytochrome P450 enzymes, Cyp), leading to the synthesis of glucocorticoids (GC). Glucocorticoids in turn suppress the activation of cytotoxic T cells and innate immune cells. LRH-1 can also be activated via the MAPK kinase (MAPK) pathway upon stimulation of growth factor receptors, such as the epidermal growth factor (EGF) receptor. In summary, our present study describes for the first time glucocorticoid synthesis in tumor cells from non-endocrine tissue and its regulatory activities on immune cells. As we recently also identified the lung mucosa as a rich source of glucocorticoids, suggesting that also lung cancer cells may be able to produce glucocorticoids, it is very likely that glucocorticoid synthesis by tumor cells is a more general mechanism of immune evasion by epithelial tumors.4

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