Comment re: Ran-GTP Control of Tumor Cell Mitosis

In Response:

In a recent work, Xia and colleagues (1) found that the small GTPase Ran is broadly overexpressed in cancer. In accordance with the emerging evidence that the Ran-GTP signaling pathway may be preferentially exploited in cancer, the authors show that it becomes essential for cell division in transformed, but not in normal, cells.

In patients with celiac disease (CD), immune response to gliadin fractions promotes an inflammatory reaction in the upper small intestine, characterized by infiltration of the lamina propria and the epithelium with chronic inflammatory cells. Moreover, adult CD patients present an overall risk of cancer that is almost twice that in the general population. These cancers include T- and B-cell non–Hodgkin’s lymphoma, oropharyngeal and esophageal adenocarcinoma, and small and large intestine, hepatobiliary system and pancreas cancers (2).

It is supposed that the overproduction of cytokines and chronic antigenic stimulation, due to gluten, plays a key role in inducing inflammation, resistance to apoptosis, and tumor development.

To better understand pathogenetic mechanisms associated with CD, we investigated the gut epithelium proteome alterations by 2D-DIGE approach (3).

We compared protein expression changes of two groups of CD patients (A and B), both with HLA DQ2 variant (4), with a control group of 5 subjects with no DQ2 or DQ8 variants and grade 0 Oberhuber modified Marsh classification (5). Group A comprised 9 patients that developed an infiltrative or hyperplastic CD (Marsh types 0, I or II), whereas group B included 5 patients with a diagnostic (destructive) lesion of CD (Marsh type III).

We observed a 2.08- and 1.83-fold increment in Ran GTPase average volume ratio in group B with respect to controls (t test $P = 0.0057$) and with respect to group A (t test $P = 0.007$), respectively. Moreover, even if comparison of Ran GTPase levels between group A and controls revealed a slight increment (1.36 t test $P = $ not significant), multigroup comparison evidenced a parallel increase of Ran levels and Marsh index (One-Way ANOVA $P = 0.015$).

Our results indicate that Ran up-regulation is not a prerogative of tumor cells but can also be linked with CD-associated chronic inflammation, intraepithelial lymphocyte infiltration, and crypt hyperplasia. Still higher levels of Ran in chronically injured tissue, at risk for local cancer development, indicate that it could have a role in tumorigenesis. Therefore, the development of a novel class of antimitotic agents, controlling a specific cell division pathway, could be useful not only for the treatment of tumors but also for chronic inflammatory disorders.

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References


©2009 American Association for Cancer Research. doi:10.1158/0008-5472.CAN-08-1270
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doi:10.1158/0008-5472.CAN-08-1270

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