

Obesity and gastrointestinal neoplasia—what are the biologic mechanisms?

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A recent review in *Gastroenterology*, by Alemán and colleagues, provides a comprehensive outline of mechanisms through which obesity may increase the risk of gastrointestinal (GI) cancers. While very plausible general concepts, such as the involvements of inflammation, growth hormone signaling, or alterations of the microbiota in cancer development are presented, direct evidence for the relative causal contributions of various types of mechanism still appears limited. Despite the increasing knowledge about the molecular basis of the obesity-cancer connection, the translation of basic research findings into cancer prevention and treatment remains challenging.

The Global Burden of Disease Study 2013 has shown that between 1980 and 2013 the prevalence of overweight and obesity worldwide has risen from 29.8% to 38.0% in women and from 28.8% to 36.9% in men (1). In parallel, epidemiological evidence that obesity is an important risk factor for many forms of cancer, including those of the GI tract, has been accumulating rapidly (2,3), along with clinical and experimental studies linking hormonal and metabolic alterations linked to adiposity (4,5) and studies linking cancer to alterations in cellular metabolism (6-8). Despite all progress, however, the mechanistic links between obesity and cancer still are only very partially understood. Given the high prevalence of obesity worldwide, unravelling the role of obesity-induced mechanisms in the etiology of cancer seems vital with respect to the identification of targets for cancer prevention and therapy (4). In a recent issue of *Gastroenterology*, Alemán and colleagues reviewed epidemiologic, clinical and experimental evidence indicating possible mechanisms linking obesity to GI cancers, including cancers of the esophagus (adenocarcinomas), stomach, colon and pancreas (9).

First sections describe general adiposity-related alterations in blood and tissue levels of glucose, insulin, IGF-I, total and bio-available sex hormones, adipokines (leptin, adiponectin) and inflammation factors, as well as possible links to the intestinal microbiota. These sections are centered around a few basic concepts. One of these is the promotion of tumor development by adiposity-related increases in hormones and growth factors (insulin, IGF-I, leptin, estrogens) that regulate cell growth, proliferation and apoptosis through ligand-specific receptors. This concept ties up closely with research findings on major cellular signaling pathways, such as the RAS/MAPK or the PI3 kinase/Akt/mammalian target of rapamycin (mTOR) pathways, which are centrally related to the control of cellular growth and proliferation and are frequently dysregulated in cancer by oncogene activation, or by inactivation of tumor suppressor genes (10,11). Another central concept is that of adiposity-related pro-inflammatory states, again mediated by the increased or decreased release of specific signaling factors from adipocytes and associated macrophages. Cellular responses to inflammation factors increasingly are being recognized as a cause of cancer, as they involve increases in the cellular production of reactive oxygen species (ROS) and nitric oxide (NO), which can cause DNA mutations (6,12). More accessorially, the authors mention recent concepts linking intestinal microbiota and endotoxemia (increased intestinal permeability, favoring translocation of microbiome-derived lipopolysaccharide to the bloodstream) to energy metabolism, obesity, inflammatory processes and tumor development.

In the following sections of their review, Alemán and colleagues summarize evidence on the possible roles of these metabolic alterations as possible mechanistic links

in the development of individual cancer types by organ site (9). In doing so, they acknowledge that between the organ sites the significance of certain pathways may differ substantially, irrespective of the validity of the more global concepts mentioned above. Regarding colorectal cancer, the authors emphasize the likely involvement particularly of insulin and IGF-I signaling, as well as of adipokines (leptin, adiponectin) and inflammation. Regarding esophageal adenocarcinomas (EAC), for which risk is associated with (abdominal) obesity much more strongly than the risk of colon cancer, the authors emphasize the role of GI reflux as causes of Barrett's esophagus and intestinal metaplasia, which are precursors to EAC. Chronic inflammation associated with esophagitis and Barrett's esophagus, along with changes in local microflora and alterations in signaling by insulin, IGF-I and adipokines are each invoked as further possible mechanistic links between obesity and EAC. For cancers of the stomach and pancreas, the available evidence for specific roles of insulin, IGF-I, adipokines or blood levels of inflammation factors appeared globally less convincing.

A large part of the evidence cited by Alemán and colleagues to support a role of signaling factors involved in growth control or inflammation is from epidemiologic studies, in which blood levels of these various peptides were associated with the occurrence of cancer or its precursor stages. A general limitation of such studies is that associations, alone, do not prove that these mechanisms are indeed causally involved. Actually, almost any marker with blood concentrations strongly related to adiposity will likely be associated with the risk of obesity-related cancers. Furthermore, many of the markers discussed (blood levels of insulin, IGF-I, adipokines, pro-inflammatory cytokines) are each correlated with BMI, and often their variations are also physiologically inter-related. This makes it very difficult to disentangle the possible independent contributions of individual markers and mechanisms to disease development (8). A further possible limitation of most epidemiologic studies is that generally metabolic markers could be measured only in blood, which may not always reflect the milieu at a local tissue level. For example, Alemán and colleagues very rightly pointed to the fact that pro-inflammatory cytokines generally have higher concentrations in visceral fat, which immediately surround the intestines, than in the sub-cutaneous fat compartments. Taken together, while proposed mechanisms are motivated by very plausible general concepts, there is little direct proof that these mechanisms are indeed causally relevant to

cancer occurrence in the general population.

Additional insight may be gained by studies examining metabolic risk factors in relation to molecular tumor sub-types characterized by different histology, somatic mutations and gene expression profiles, and by examining the effects of certain medications, alone or in interaction with BMI. For example, it has been a long-standing hypothesis that elevated estrogens could protect against colon cancer. Support for this hypothesis has come from studies showing a reduced risk of colon cancer among women using oral contraceptives (13) or menopausal hormone therapy (MHT) (14), and showing that for MHT users this reduction is stronger for postmenopausal women with lower BMI, who generally also have lower endogenous estrogen levels (15). Furthermore, a large case-control study, in which colonic tumor samples were collected and analyzed, showed that the reduction in risk for users of exogenous estrogens was restricted to tumors expressing estrogen receptor- β (ESR2), while it was not observed for ESR2-negative tumors (16). Taken together these observations suggest that estrogens may in fact confer protection against colon cancer (14).

With respect to insulin and glucose metabolism, several randomized controlled trials that are underway may help answering the question if metformin—a glucose and insulin lowering drug—has beneficial effects among non-diabetics (17). Another group of drugs of particular relevance for the further clarification of the role of IGF-1 signaling in cancer development are inhibitors of the mTOR, of which IGF-I is a positive regulator. However, a strong impact of mTOR inhibitors on obesity-related cancers remains to be demonstrated (18). Also, the application of IGF-I receptor inhibitors has shown disappointing results (19). This underlines the difficulty of translating the basic research findings outlined by Alemán *et al.* into therapeutic options. Concerning the inflammatory component of obesity presented by Alemán *et al.*, existing evidence from trials on aspirin is intriguing, as post hoc analyses of RCTs strongly suggest that its use reduces the risk of GI cancers (20). However, basic research revealed that anti-platelet actions of aspirin may play a more important role than its anti-inflammatory actions in cancer prevention (20). In turn, considering that obesity induces thrombosis (21), these findings imply that other mechanisms in addition or complementary to those described by Alemán *et al.* may constitute the obesity-cancer connection.

Adipokines, such as leptin or adiponectin have consistently been associated with cancer development in basic science and

epidemiological studies (22), which may point to a role of such factors as promising drug targets (23). In this context, however, findings from a recent Mendelian randomization study on adiponectin and diabetes risk seem important (24). While pleiotropic anti-diabetic properties had also been proposed, polymorphisms used as unconfounded proxies of adiponectin were not associated with diabetes risk in a large sample including some 16,000 diabetes cases, and a causal relationship between adiponectin and diabetes seems questionable (24). This finding illustrates, that causal associations between adipokines and cancer may not necessarily exist, even in case of consistent findings from mechanistic studies and observational epidemiology, and that it cannot be ruled out that factors such as adiponectin or leptin are bystanders of obesity rather than modulators of carcinogenesis.

Finally, Alemán *et al.* referred to connections between the composition of the gut microbiota with obesity and development of GI cancers (9). Changes in the microbiota could be responsible for an altered caloric salvage, thus directly regulating weight gain. In addition, a long standing theory suggests that particular toxins or metabolites of microbes such as secondary bile acids may exert carcinogenic effects in the colon, whereas others such as butyrate may be protective (25). Inflammation due to alterations in the microbiota induced by obesity is another potential pathway leading to GI cancer (26). While these proposed mechanisms seem plausible links between obesity and GI cancer risk, the identification of specific microbes and microbial metabolites or enzymes implicated in cancer development definitively requires further research. At this point in time the utility of targeted interventions to modify the gut microbiota via dietary regimen, anti- and probiotics, or fecal transplantation with respect to cancer is largely unclear, even though these approaches are theoretically appealing (27,28).

Overall, the review by Alemán *et al.* describes well the complexity of several obesity-induced physiologic dysregulations, which have many physiologic interrelationships and have many facets that can be conceivably linked to cellular processes potentially involved in tumor development. The importance of the presented mechanisms may substantially differ for different types of GI, by organ site and molecular tumor sub-type. Data from trials on widely used drugs point to a possible benefit of metformin and particularly NSAIDs in the prevention of GI tract cancers, which may imply a crucial role of chronic inflammation and insulin and/or IGF-I signaling in their

development. Up-regulated estrogen signaling could protect against colorectal cancer, although further studies are needed to confirm this potential link. The same is true with regard to adipokines, such as adiponectin or leptin, for which a role as causal factors in cancer development remains to be established. The gut microbiota is an exciting field of study for the prevention of GI cancers, but a better understanding of the pathways involved is required, and the outcomes of interventions to manipulate its composition are surely of special interest.

The example of a potential relationship between obesity, platelet aggregation and GI cancers that has been proposed based on findings from meta-analyses on NSAID use and cancer risk indicates that mechanisms additional to the ones discussed by Alemán *et al.* also deserve further study. Thus, and in view of the complex interplay, the potential site- and subtype-specificity as well as the stage dependency of the mechanisms to link obesity and cancer, one might argue that, despite our improved understanding of the underlying biological phenomena, a targeted therapeutic exploitation of obesity-induced pathways involved in cancer development may not easily be achieved (8). Against this background, it appears that primary prevention measures against the environmental causes of obesity remain of utmost priority.

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