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RESEARCH HIGHLIGHT

When mutant p53 fires up

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Mutant p53 functions as a key molecular element in the inflamed colon tissue joining forces with nuclear factor kappa-B (NF-κB) to prolong and intensify the inflammatory response, leading eventually to a higher risk for colitis associated colorectal cancer (CAC). This phenomenon coincides with the fact that mutations in p53 are an initiating factor of CAC unlike sporadic colorectal cancer (CRC) where they are considered a late event contributing to tumor progression. This research highlight attempts to illuminate the consequences of such a reshuffling in the molecular sequence of events from non-cancerous tissue to invasive carcinoma of the colon. Implications of this different role taken by mutant p53 when inflammation is involved might affect tumorigenesis, pathogenesis, and hierarchical morphogenesis and suggest the reevaluation of current animal models used to study CAC. We also discuss the possible role of mutant p53 in stromal and immune compartments, either in an autonomous or non-autonomous manner.

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The monolayered epithelia of the intestine have to maintain a constant delicate balance, taking into account radical changes at the luminal end. Throughout this continuous battle, which involves exposure to harsh mechanical, chemical and biological conditions, the intestinal epithelium is required to juggle between the absorption of nutrients and metabolites while restricting the penetration of unwelcome infectious agents [1, 2]. Not surprisingly, meticulous multifaceted regulation plays a major role in this fragile equilibrium and several homeostasis-preserving mechanisms are in place to ensure it, including mucin secretion by goblet cells, antimicrobial activity of Paneth cells and high turnover rate of villus enterocytes. To that end, signals originating in the stromal and immune compartments, as well as from commensal bacteria, are channeled to the stem cell-containing niche of the intestinal crypt, the "headquarters" of the tissue, where a dynamic "tango" between the Wnt and the BMP signaling pathways dictates the proliferation/differentiation balance [3, 4]. Importantly, a high apoptotic rate resulting in constant tissue renewal, coinciding with high levels of oxidative stress and free radicals, add up to an increased risk of DNA damage that might lead to neoplastic cell transformation. This mutagenic risk becomes even more threatening under chronic inflammatory conditions, which increase DNA damage and allow pathogenic bacteria to take over the commensal population of the microbiota, thus exposing the epithelium to yet another potentially oncogenic factor [5, 6].

On top of the environmental factors that increase the risk of colorectal cancer, genetic predisposition also plays a major role. One of the most prominent examples is the Adenomatous polyposis coli (*APC*) gene, which functions as a negative regulator of the Wnt pathway.

Mutation or loss of *APC* is often the initiating genetic event in colonic tumorigenesis, as demonstrated robustly in familial adenomatous polyposis (FAP) [7, 8]. Interestingly, deregulation of the Wnt pathway by mutation of either *APC* or β-catenin is found in more than 90% of sporadic colorectal cancer (CRC) cases and can be identified early on in the vast majority of them[9, 10]. Notwithstanding, in order for the carcinogenic process to be fulfilled in the colon, accumulation of additional genetic and epigenetic alterations must occur, commonly involving mutations in K-Ras as well as increased microsatellite instability (MSI) and aberrant methylation patterns. Another profound characteristic of full-blown CRC is the high abundance of p53 mutations, whose late appearance in this type of cancer suggests a role in promoting cell invasion and pre-metastatic contribution [11]. Indeed, such oncogenic activities were found to be part of the "gain-of-function" acquired by specific p53 mutants [12, 13], which might enable the adenomatous lesion to progress into invasive carcinoma.

Strikingly, this sequence of tumorigenic events seems to get reshuffled in patients suffering from inflammatory bowel disease (IBD), eventually resulting in colitis-associated colorectal carcinoma (CAC)[14, 15]. A higher frequency of p53 mutations occurs early in the inflamed tissue of those patients, at a time when cancerous lesions are not yet observed, indicating a shift in the role of such mutations from a late promoting factor to an initiating event governing CAC and determining its development [16, 17]. Moreover, unlike in sporadic CRC, the incidence of APC mutations is relatively low in CAC, and those mutations mostly occur at later stage of the disease, reinforcing the notion that APC is no longer in the driver's seat when colitis becomes a major player [18, 19]. Of note, adenomatous polyps are not observed in a substantial fraction of CAC, and instead one can observe escalating grades of flat dysplastic lesions progressing to invasive carcinoma.

The similarity in many aspects of colon tumorigenesis between humans and rodents, both at the molecular and the pathological levels, has generated ample efforts to model this malignancy in mice and rats [20]. Some of the frequently used protocols employ azoxymethane (AOM), a carcinogen whose mechanism of action involves DNA base changes from G:C to A:T [21]. When injected into the peritoneum AOM affects the colon (primarily its distal end), eventually leading to cytoplasmic and nuclear accumulation of β-catenin as a result of mutations in the *APC* and β-catenin genes. Due to the aberrant activation of the Wnt pathway, yielding a high rate of adenomas in mice and rats, the AOM model has become a common model to study CRC. On the other hand, CAC is typically modeled in rodents exposed to a combination of AOM with colitis-inducing agents such as dextran sodium sulfate (DSS) [22, 23]. Uptake of DSS, dissolved in the drinking water, damages the intestinal epithelial barrier, forming ulcers resembling to the ones found in ulcerative colitis, thus allowing an interaction between the microbiota and the immune system of the host triggering an inflammatory response. The fact that the combination of AOM with DSS strongly shortens tumor latency, together with the pronounced manifestation of chronic inflammation, have popularized this model and caused it to be considered a definitive proof for the link between cancer and inflammation. Nevertheless, the remarkable efficiency of AOM/DSS is compromised by the notion that, similarly to the APC/min mouse model, practically all treated animals acquire either APC or β-catenin mutations[21], channeling the carcinogenic process through a progression path that presumably disregards p53 mutations.

Guided by the realization that early p53 mutations in the inflamed colon potentially serve as initiating events in human CAC, we opted to combine mutant p53 (mutp53) and chronic inflammation as two predisposing conditions in a mouse model of colitis [24]. Specifically, mice constitutively expressing mutp53 (mutp53 "knock-in" mice) were exposed to DSS and were and monitored for colitis and cancer development. Strikingly, when mutp53 was present *a priori*, addition of a carcinogen (AOM) became dispensable, and cancer emerged in almost all mice upon treatment with DSS alone. Remarkably, the histopathological pattern consisted exclusively of non-polypous flat dysplastic lesions, which progressed gradually and eventually invaded the muscularis mucosa and acquired distinctive features of mucinous adenocarcinoma. Intriguingly, when mutp53 mice were treated with AOM + DSS such flat dysplasic lesions were not observed. In fact, such combined treatment elicited polyps at a rate that was practically indistinguishable from that seen in wild type mice. This dramatic difference in outcome was completely dependent on the presence or absence of AOM, leading to the conclusion that whenever this carcinogen is part of the experimental model, the colon is bound to display features commonly associated with sporadic colorectal carcinogenesis, regardless of p53 mutation status. This conclusion was further reinforced by the finding that β-catenin appeared to be confined to the plasma membrane in cancerous areas of mutp53 mice treated with DSS only, while becoming cytosolic and nuclear in the adenomas of AOM/DSS treated mice, indicative of Wnt pathway mutational activation.

The above study further indicated that p53 gain-of-function mutations contribute to CAC by augmenting and prolonging NF-κB activation[24] Future

CAC research in mouse models must take into account the fact that any model involving early defects in the Wnt pathway will most likely reflect the sporadic/familial colorectal cancer pattern rather than the IBD-associated pattern. Since the existence of early p53 mutations in IBD patients is a key factor, it should not be overlooked. Disconnecting between APC or β-catenin aberrations and the early onset of smoldering inflammation in the colon tissue will help to better understand the processes that drive CAC. Including mutp53 as an initiating event will therefore mimic more faithfully the course of the disease in human patients.

On the same note, this "game of thrones" between mutp53 and Wnt pathway deregulation might also play an intriguing role in the pathogenesis of colon tumors. Despite the fact that the intestinal stem cells reside very close to the bottom of the colonic crypt [25], a considerable fraction of colon tumors may originate from higher regions of the crypt that are comprised of more differentiated enterocytes [26]. This "Top-down" formation of de-novo crypts collides with the perception that tumors are likely to arise from unleashed expansion of the stem cells in a "bottom-up" manner [27]. In another recent publication, [28] Schwitalla and colleagues proposed a possible explanation for this conflict, claiming that both morphogenic patterns do not contradict each other and rely on the extent of the Wnt activation, following previous reports suggesting that the characteristics and intensity of the Wnt-driven tumorigenesis are determined by the specificity of APC mutations and its loss of heterozygosity (LOH)[29, 30] . It appears that a fine cross-talk between NF-κB and β-catenin controls the volume of Wnt activation leading to a "bottom-up" type of phatogenesis in lower levels but encourages transformation and carcinogenesis in $LGR5^-$ epithelial cells when Wnt levels are elevated to a higher extent. The central role played by NF-κB, particularly stimulated by TNF-α, gives rise to an intriguing question regarding the part taken by mutp53 in this delicate balance. The mutual interaction between NF-κB and mutp53 was shown in our study to be a central feature of the inflamed colon both in mice and humans and TNF-α was, again, considered to be a major mediator [24]. It is therefore tempting to examine the impact that the emergence of p53 mutations will have on the ability of NF-κB to stabilize mutant β-catenin in different regions of the crypt. Considering that in CAC, where mutp53 is expected to be found at early stages, the adenoma-carcinoma axis is not the mainstream as in CRC, together with the observation that the lesions tend to be more flat, it will be hard to determine if mutp53 will tilt the "bottom-up"/ "top-down" balance to a certain direction. Since Intestinal crypts are monoclonal in origin, contributing to their strict hierarchical fashion, it may be possible to distinguish between transformed glands which harbor mutp53 and such that do not bear p53 mutations. If indeed the presence of mutp53 promotes any morphogenic development it might expose a fascinating interplay shared by mutp53 and LGR5+ intestinal stem cells on the background of colitis and conditions that favor increased DNA damage.

Apart from the obvious discussion focusing on the intestinal epithelial cells and the significance of p53 mutations by preceding conditions of stress and inflammation or by cryptal topography, the non-epithelial compartment of the colon tissue might also be affected. This idea could be examined from two different angles: the possible accumulation of mutp53 in any non-epithelial cell residing in the tissue as oppose to p53 mutations in the epithelia that yield a non-autonomous effect on neighboring stromal and immune cells.

Hints for both options were found during this study as well as in previous reports by others [24, 31-33]. A robust evident was presented when bone-marrow (BM) chimeric mice were challenged with DSS and monitored for their inflammatory score. Mice that carried mutp53 only in their BM (transplanted into WT p53 animals) still showed an increased susceptibility to DSS compared with WT p53 animals reconstituted with WT BM. This effect was not as pronounced as the one observed in the whole mutp53 animal which was transplanted with mutp53 BM but was considerably significant, given the fact that the entire epithelial compartment is WT in these mice. Furthermore, the opposite experiment revealed that when mutp53 chimeric mice are reconstituted with WT p53 BM, the DSS effect is attenuated to a significant extent. Both complementary tests suggest an active role which could be played by p53 mutations in the immune cells. In parallel, when intense accumulation of mutp53 was detected in CAC sections taken from both mice and humans, it was found to be correlated with nuclear NF-κB (p65) in the epithelia but also in adjacent fibroblasts and immune cells. According to the lack of p21 expression in these sections, the stabilized form of p53 in the cells is mutated but further and more accurate confirmation is required.

The possibility that mutations in p53 do occur in stromal and immune compartments in a clonal manner which leads to selective advantage of such cells has been a source for many debates throughout the recent years. The studies showing elevated immuneohistochemical staining in non-epithelial p53 as well as those presenting high prevalence of sequenced mutations in such compartments [34, 35], are criticized for not providing an adequate method to accurately distinguish between

stromal and epithelial p53 mutations. Furthermore, other reports actually contradict the existence of such mutations in cells which are not part of the epithelia and reclaim the notion that mutp53 gains function only in the cells that are prone to become cancerous [36]. However, as mentioned above, after decades of research focusing in the autonomous roles of both the WT and the mutant forms of p53, accumulated data now adds-up to reveal a non-autonomous impact forming a local paracrine influence on neighboring cells [37] [38]. Given the ability of WT p53 to induce tumor suppressive activities presumably via secretory or exosomal elements, it is plausible to assume that epithelial cells harboring mutp53 will acquire similar properties and use cellular mechanisms to recruit the adjacent stoma and immune cells in attempt to benefit a selective advantage promoting neoplasia. We believe that the cornerstones for such a possibility have been set, but still require an additional thorough scientific effort providing a clear answer. For that purpose, a use of inducible and tissue specific mutp53 animals may become a valuable tool delaminating the impact p53 mutations in each compartment as for their contribution to the tumorigenesis of the tissue.

In this short research highlight we attempted to illuminate a few crucial insights putting mutp53 as an anchor factor in colitis that develops into CAC potentially affecting fundamental elements as the molecular tumorigenesis, pathogenesis, and hierarchical morphogenesis. Joining forces with NF-κB at early stages was also suggested herein to be part of an intense cross-talk between the tumor cells and other cells within the tissue contributing to tumor prosperity. Additional research involving animal models as well as clinical samples will definitely shed more light on this fascinating connection that lies in the basis of CAC and deeper understanding of it will surely be beneficial for CAC patients.

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