A new era for understanding genetic evolution of multistep carcinogenesis

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Received: 20 March 2019 / Accepted: 22 March 2019 / Published online: 28 March 2019
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Abstract Cancer development is a multistep process involving genetic and cellular alterations, and recent advances in next-generation sequencing have elucidated mutation landscapes of premalignant lesions as well as early- and late-stage tumors. In this issue of *Journal of Gastroenterology*, Kim and colleagues contributed to the better understanding of genetic events in putative precursors of hepatocellular carcinoma (HCC). Precancerous tissues are divided into canonical and non-canonical types, which share common driver mutations with cancerous lesions or not, and potential gatekeeper gene(s) for clonal selection play a critical role in driving precursors to cancers not only in HCC, but also in esophageal, gastric, colorectal, and pancreatic cancers.

Keywords Multistep carcinogenesis · Genetic evolution · Hepatocellular carcinoma · Regenerative nodule · TERT promoter mutation · Premalignant lesions

Cancer development is a multistep process involving genetic and cellular alterations, and recent advances in next-generation sequencing (NGS) have elucidated mutation landscapes of premalignant lesions as well as early- and late-stage tumors. In this issue of *Journal of Gastroenterology*, Kim et al. [1] contributed to the better understanding of genetic events in putative precursors of hepatocellular carcinoma (HCC).

An International Working Party of the World Congresses of Gastroenterology proposed a consensus nomenclature and diagnostic criteria for hepatocellular nodular lesions, which are categorized into large regenerative nodule, low-grade dysplastic nodule, high-grade dysplastic nodule and HCC [2]. Kim et al. highlighted precancerous genetic aberrations in regenerative nodule (RN), and performed genomic sequencing of 205 RNs and 7 HCCs collected from 10 patients who underwent living-donor liver transplantation. Each RN harbored somatic mutations with high variant allele frequency, indicating clonal expansion of parental hepatocytes. Although mutation signature of RN was closely similar to that of HCC, namely a unique predominance of C > T, T > C and C > A mutations (35, 25 and 14%, respectively), mean somatic mutation rate in RN was tenfold lower than that in HCC (0.22/Mb vs. 2.8/Mb). Significant copy number alterations were also undetectable in RN, whereas gain of chromosome 5p (*TERT*) and loss of chromosome 1p (*ARID1A*) and 17p (*TP53*) were generally observed in HCC. Targeted sequencing discovered 51 non-silent mutations in 47 of 205 RNs, which included two missense mutations in the *TP53* gene. Of note, *ARID1A* and *ARID2*, encoding key components of the SWI/SNF chromatin remodeling complex, were mutated in six and three RNs, respectively, but not *TERT* promoter in any RN. These intriguing results provide two important suggestions: (i) somatic mutations in genes associated with the chromatin remodeling are the earliest genetic events in pre-neoplastic lesions of the liver; (ii) *TERT* promoter mutation is the initial and essential step for hepatocellular carcinogenesis, because the mutation frequency increases during the stepwise progression from dysplastic nodule (DN) to HCC as previously reported [3, 4].

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With the advent of deep sequencing, the genetic evolution of multistep carcinogenesis in the digestive system is just now being revealed. Expectedly, whole-exome sequencing for colorectal adenoma clarified that *APC* was the most frequent mutated gene (45.7%), and additional targeted sequencing identified the absence of somatic mutations in *SMAD4* and *PIK3CA* in adenoma and the trend of mutation prevalence in *APC*, *KRAS*, *TP53*, *SMAD4* and *PIK3CA* toward colorectal cancer [5]. Three different groups have discovered *KRAS* active mutations in 90% of pancreatic intraepithelial neoplasia (PanIN) lesions and no non-synonymous mutations in *SMAD4* gene using the cell samples isolated by laser capture microdissection [6–8]. Intestinal metaplasia, a preceding condition of gastric cancer, exhibited low mutation burdens, recurrent mutations in *FBXW7* (4.7%), but not in *TP53* or *ARID1A*, and only chromosome 8q (*MYC*) amplifications in contrast to gastric cancer [9]. Esophageal adenocarcinoma arises from Barrett's esophagus, and the most prevalent gene mutations in the cancerous tissues were present at similar frequency in the non-cancerous tissues, including in *ARID1A* (10%) and *SMARCA4* (5%) [10]. Only *TP53* and *SMAD4* demonstrated distinct mutation rates between disease stages; *TP53* was mutated in both high-grade dysplasia (72%) and esophageal adenocarcinoma (69%) but rarely in Barrett's esophagus (2.5%), and *SMAD4* mutations were detected only in the tumor samples (13%). Targeted deep sequencing of 157 normal esophageal epithelia and 519 esophageal squamous cell carcinomas showed marked overrepresentation of somatic mutations in NOTCH family genes in the normal tissues (*NOTCH1*, 66.2% vs. 15.0%) [11].

These emerging findings lead to two plausible hypotheses of genetic evolution in carcinogenesis. One is that precancerous lesions can be divided into canonical and non-canonical types, which share common driver mutations with cancerous lesions or not. The canonical type is composed of colorectal adenoma (*APC*), PanIN (*KRAS*) and Barrett's esophagus (*ARID1A* and *SMARCA4*), while the non-canonical type is composed of intestinal metaplasia (*FBXW7*) and normal esophagus mucosa (*NOTCH1*). Since both RN and HCC have frequent mutations in the SWI/SNF chromatin remodeling factors (*ARID1A* and *ARID2*), RN is placed in the canonical type. The other is that driver mutations can be accumulated step by step during malignant transformation from normal cells to cancer cells. Taken together with previous studies, *SMAD4* is a potential gatekeeper gene for clonal selection in various types of gastrointestinal cancer including colorectal cancer, pancreatic cancer and esophageal adenocarcinoma. In hepatocellular nodular lesions, *TERT* promoter mutation plays a critical role in driving RN to DN and HCC as described above.

We have reached the time when we can determine genetic changes in each stage of cancer as well as classify each sample of tumor into molecular subtypes with NGS technology [12]. The next challenge is to develop novel tools for early detection and prophylactic agents targeting driver pathways.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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