Introduction to Miniseries on DNA and Cancer

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This special miniseries on cancer includes two reviews. The first one, by Drs François Ghiringhelli and Lionel Apetoh, analyzes the impact of 5-fluorouracil (5-FU) on anticancer immune responses.[1] The second review, by Drs. Michael Burns, Brandon Leonard, and Reuben Harris, describes the properties of the DNA cytosine deaminase, APOBEC3B, which converts cytosine to uracil and may be responsible for various mutations in human cancers.[2]

In the first review, "Enhancing the anticancer effects of 5-fluorouracil: Current challenges and future perspectives," Drs Ghiringhelli and Apetoh describe the biological mechanisms stimulated by 5-FU to potentiate anticancer immune responses. The 5-FU inhibits DNA and RNA synthesis, leading to cancer cell death. While chemotherapies kill cancer cells and are believed to induce immunosuppression, several groups and the authors of this review have shown that, in fact, anticancer immune responses are triggered by types of chemotherapy and contribute to the success of these drugs. In their remarkable review, the authors analyze the different mechanisms which stimulate several anticancer pathways. Thus, 5-FU increases tumor cell destruction by natural killer (NK) and $CD8^+$ T cells by stimulating the expression of NKG2D ligands and Fas. In addition, 5-FU reduces the number of myeloid-derived suppressor cells (MDSC), but not the levels of regulatory T (T_{reg}) cells. The authors demonstrate that the toxic effect of 5-FU is selective and is due to the low level of thymidylate synthase expressed in MDSC as compared to other T, B, and NK cells. However, while 5-FU can trigger cancer cell death directly, its anticancer properties are modest *in vivo*. Thus, the authors analyzed studies of several groups that have associated 5-FU with other cytokines to upregulate the anticancer effect *in vivo*. IL-12, IL-15, IFN-α, and Flt3 had been used in combination with 5-FU successfully and could potentiate anti-tumoral immune responses. In the last part of their review, the authors analyze their own attempts to increase the anticancer effects of 5-FU and describe the complex biological pathways that are involved in tumor growth.

In the second review entitled "APOBEC3B: Pathological consequences of an innate immune DNA mutator," the authors introduce the APOBEC family and describe the physiological functions of APOBEC3 members in innate immunity. Using a very good iconography, the authors depict the enzymatic activity of APOBEC members, which catalyze the hydrolysis of cytosine to uracil in single-stranded DNA, and the potential mutagenic outcomes of uracil lesions. The authors analyze the evidence showing that APOBEC3B is involved in human cancer and the impact of this enzyme in promoting genetic heterogeneity. Finally, the authors present the results from different groups suggesting that *APOBEC3B* overexpression and mutagenesis are stimulated by an antiviral response against the human papillomavirus in cervical and head/neck cancers. This review suggests that increasing or decreasing *APOBEC3B* mutagenesis in *APOBEC3B*-expressing cells may stimulate tumor cell death through various mechanisms.

These two complementary reviews thus highlight the importance of chemotherapy or enzymes targeting DNA or RNA integrity in strategies to eradicate cancer growth.

REFERENCES

1. Ghiringhelli F, Apetoh L. Enhancing the Anticancer Effects of 5-Fluorouracil: Current Challenges and Future Perspectives. Biomed J 2015;38:111-6.
2. Burns MB, Leonard B, Harris RS. APOBEC3B: Pathological Consequences of an Innate Immune DNA Mutator. Biomed J 2015;38:102-10.

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