T cell fat catabolism: A novel target for kynurenine?

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Tumors accumulate metabolites that deactivate infiltrating immune cells and polarize them toward anti-inflammatory phenotypes. Complex networks are orchestrated by several of the most potent immunosuppressive metabolites, including adenosine, kynurenines, prostaglandin E2, and norepinephrine and epinephrine. Although retrospective analyses of clinical data have elucidated that their activity is negatively associated with prognosis in diverse cancer indications, the overall scenario is still unclear, and there occurs a paucity of approved therapies that disrupt their synthesis or downstream signaling axes.[1]

The kynurenine pathway has been proposed as one of the key mechanisms used by tumor cells to escape immune surveillance for proliferation and metastasis. In an inflammatory environment such as cancer, the pathway is considered to be elevated, suppressing local immune cell populations and enhancing tumor growth. Both glioblastoma and hepatocellular carcinoma are considered prototypical examples of this condition.

The paper by Siska et al, appearing in this issue of EBioMedicine[2] shows two novel pieces of information regarding the role of the amino acid kynurenine (a byproduct of tryptophan catabolism, which contributes to immune homeostasis) in cancer versus nononcologic conditions. Firstly, using the D-kynurenine isomer, the authors demonstrate a novel mechanism of action of kynurenine which involves induction of T-cell apoptosis, a long-established effect, mostly described for other tryptophan metabolites, including quinolinic acid and anthranilic acid.[3] This new mechanism involves increased β-fatty acid oxidation and depletion.

As a matter of fact, the regulatory effects of tryptophan metabolites could contribute to immunoregulation or immunosuppression, thus protecting from hyperinflammatory and autoimmune responses.[4,5] Yet, those metabolites might likewise result in suppression of antitumor activity, under conditions dominated by overproduction of those metabolites by tumoral tissues.[6,7] In this scenario, the study suggests that, based on qualitative and quantitative measurements, the contribution of kynurenine to the suppression of anti-tumour immunity might have been overestimated in some previous studies. In particular, human tumour kynurenine concentrations were found only in the low micromolar range, far below the required 1 mM L- or D-kynurenine needed to induce T cell apoptosis in vitro.

Using an experimental model system of colitis, and in a mismatched cardiac allograft rejection model as well, the authors investigated D-kynurenine for potential supplemental immunosuppressive therapy, administering the former so as to reach tissue and serum kynurenine concentrations at or above those of human cancer patients. While D-kynurenine protected mice from autoimmune colitis in an Aryl hydrocarbon. Receptor-dependent manner, the same metabolite failed to meet the challenge of more stringent conditions, such as those involving mismatched cardiac allograft rejection.

Overall, although tryptophan-catabolic enzymes may have non-enzymatic immunosuppressive effects independent of kynurenine in glioblastoma,[8] it is reasonable to assume that low micromolar tumour kynurenine concentrations may have limited immunosuppressive effects and conversely more immunoregulatory actions. In addition, although not explored in the present study, tumour cells may activate additional pathways that may suppress the immunoregulatory effects of kynurenine altering also fatty acid composition in immune cells.

It is, however, to be noted that, in most experimental models, it is not the mere accumulation of kynurenine that matters so much as the combined effects of tryptophan starvation and tryptophan catabolites that activate the systemic response of Aryl hydrocarbon Receptor-driven generation of T regulatory cells, in addition to reducing T cell receptor zeta-chain expression.[9] Thus, there might still occur more subtle regulatory effects of kynurenine not fully explored by this article. Furthermore, Kynurenine 3-monooxygenase (KMO) is the pivotal enzyme in the kynurenine pathway which degrades kynurenine. Overexpressed by cancer cells,[10] this enzyme may have contributed to blunting the effect of supplemental immunosuppressive therapy in the Authors' setting.

In conclusion, the paper by Siska et al.[2] provides evidence that kynurenine affect T cell lipid catabolism and have a demonstratable yet limited immunosuppressive effects in vivo in specific settings. This could reasonably account for the observed inefficacy of tryptophan catabolic enzyme inhibitors in human cancer trials, and may help reconsider or refine the current strategies by patient stratification based on actual kynurenine levels, and presence of kynurenine degrading enzymes so as to

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optimize the actual clinical value of the efforts in this direction.

Declaration of interests

None.

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