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Harnessing systemic immune responses for polyomavirus BK involvement in cancer development and progression

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Dear Editor,

In the manuscript entitled “Tumor growth factor- β is an important factor for immunosuppression and tumorigenesis in Polyoma BK virus infection; a systematic review article” Ashraf Kariminik and Babak Kheirkhah stress an interesting point about the role of TGF- β in the development of polyomavirus BK (BKPyV)-related human malignancies [1]. However, in order to better define the interplay between BKPyV carcinogenesis in human and TGF- β activity, some passages of this manuscript need to be discussed. The authors state that the oncogenic activity of BKPyV is regulated by TGF- β . It is worth noting that TGF- β is mainly a tumor promoter “*per se*” in advanced stages [2], while its role as a tumor suppressor at early stages of cancer formation [3] contradicts the review’s claim, if we assume that BKPyV-driven carcinogenesis develops at pre-early cancer stages. In addition, studies cited by the authors to support the link between the cytokine and the virus have been carried out either *in vitro* or *in vivo* in animals. For this reason, WHO classified BKPyV as *possibly* carcinogenic in human (group 2A; <http://monographs.iarc.fr/ENG/Monograph/vol104/mono104.php>). These studies are mostly using the middle T oncogene, which is expressed in murine but not in human polyomaviruses. Last but not least, the assertion “the higher the viral load, the higher the risk of cancer development” is misleading because cancer transformation can occur in infected cells during the latent state of BKPyV due to abortive infections [4]. In BKPyV-related human cancer, the established regulatory environment characterizing these malignancies might be maintained or enhanced by BKPyV. We have recently reported that the main regulatory protein

LTag was able to reactivate regulatory T cells expressing and releasing both IL-10 and TGF- β in BKPyV seropositive prostate cancer patients with BKPyV positive lesions and an aggressive phenotype [5]. Therefore, to interpret the existing relationship between TGF- β and BKPyV in cancer development, the virus as enhancer of an established regulatory tumor microenvironment needs to be factored in.

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