Expression of mTOR-signalling pathway proteins in skin squamous-cell carcinomas before and after conversion to mTOR-inhibitors

Inhibitors of the Mammalian Target of Rapamycin (mTORis) are drugs exerting both immunosuppressive and antitumor effects, and are thereby used in organ-transplant recipients (OTR) in order to both prevent allograft rejection and to reduce the risk of skin tumor development in these patients. We studied the effects of mTORis on the expression of proteins of the mTOR pathway in cutaneous squamous-cell carcinomas (cSCC) developing in OTR, before and after they were switched to mTORis.

An immunohistochemical study was performed on formalin-fixed, paraffin-embedded specimens of 23 cSCC retrieved from the files of the Pathology Department, Ed. Herriot Hospital Group, Lyon, France. These tumors had been excised from 10 OTR who had developed post-transplant cSCC, and who had been switched to mTORis in order to prevent further carcinoma development. Twelve out of the 23 (52%) tumors were cSCC developed before switching to mTORis, whereas the remaining 11 ones (48%) had developed after conversion to mTORis. The diagnosis of all tumors had been confirmed by histological examination. The majority (70%) of cSCC were well-differentiated, 5 were moderately-differentiated and 2 were poorly-differentiated. Immunohistochemistry was performed on sections from each cSCC with antibodies against pAkt, pmTOR and PI3K proteins according to a standard streptavidin-biotin-immunoperoxidase technique with diaminobenzidine as chromogen and Mayer's hematoxylin as counterstain. cSCC were considered positive if at least 10% of tumor cells expressed the examined protein. Statistical comparison was made with the chi-square test, with a *p*-value of 0.05 or less considered significant.

The expression of pmTOR was cytoplasmic and was observed in 8/12 (67%) cSCC that had developed before, and in 8/11 (73%) cSCC that had developed after, switch to mTORis ($p>0.05$). Eleven out of 16 (69%) pmTOR-positive cSCC were well-differentiated and 5 (31%) were poorly- or moderately- differentiated. Most (5/7, 71%) of the pmTOR-negative cSCC cases were well-differentiated. Overall, the pmTOR expression did not show obvious correlation with tumor differentiation. pAkt immunoreactivity was observed both in the cytoplasm and the nucleus of the cSCC cells, whereas PI3K expression was found only in the cytoplasm. All cSCC cases in both groups (pre- and post-conversion) expressed pAkt, and all but two (one in each group) were positive for PI3K. No statistically significant differences were found in pAkt and PI3K expression between pre- and post-switch SCC cases ($p>0.05$). These results suggest that cSCC may develop in OTR, even after mTORis administration. At the protein level, the molecules participating in the AKT-PI3K-mTOR pathway are expressed both before and after mTORis administration in OTR patients, at least as confirmed by immunohistochemistry for phosphorylated forms of mTOR and AKT. These findings suggest an activation of the pathway despite the administration mTORis, which could be anticipated considering the development of new cSCC under mTORis. Although

mTORis are effective in reducing the rate of new cSCC development in OTR, they do not totally suppress skin carcinogenesis and specifically new cSCC development. We speculate that this could be due to activation of other, parallel signaling pathways, highlighting the need for combination treatments targeting several pathways for a more efficient tumor prevention. Further studies, namely on molecules downstream of the mTOR inhibition, cellular feedback systems or parallel signaling pathways, will hopefully help unravel the molecular mechanisms whereby mTORis reduce skin carcinogenesis in OTR.

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Publication

mTOR Signalling Pathway-protein Expression in Post-transplant Cutaneous Squamous-cell Carcinomas Before and After Conversion to mTOR-inhibitors.
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Anticancer Res. 2018 Jun