Abstract # 320

MDSC Trafficking and Function in RCC by CXC4R in the Presence of a VEGF-R Antagonist is Dependent on HIF-2α Expression

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Background: In murine xenografts using human RCC 766 and 786 cell lines, we have previously demonstrated that acquired resistance to the VEGF antagonists sunitinib and axitinib are associated with a marked decrease in the expression of COX2 and/or iNOS, resulting in decreased expression of the major micro-RNA (miR) targets miR-30a and miR-30c. Additionally, CXC4R1, the receptor for SDF-1/CXCL12, is over-expressed by RCC cells. As a result, the expression of miR-30a and miR-30c is regulated in a feedback loop by the HIF-2α transcription factor. In this study, the role of miR-30a and miR-30c in RCC xenografts to the VEGF antagonists sunitinib and axitinib was associated with a marked increase in the infiltration of CD11b+/Gr-1+ myeloid-derived suppressor cells (MDSC). MDSC express CXCR4 and its ligand, SDF-1/CXCL12, is produced in response to hypoxia induced by the VEGF antagonists. We have previously reported that both in vitro and resistance to axitinib could be prevented by concurrent administration of X4P-001 (a CXCR4 antagonist).

Introduction: To investigate the early effects of inhibiting MDSC trafficking with respect to CXC4R antagonists, we sought to identify the resistance mechanism in RCC xenografts to the VEGF antagonists sunitinib and axitinib. MDSC trafficking to the tumor was significantly increased both in vitro and in vivo upon treatment with the VEGF antagonists, resulting in an anti-angiogenic effect of the combination. Concomitantly, treatment with both agents alone had an increase in CD11b+ positive tumor cells as early as Day 3, which did not occur in the combined treatment with X4P-001 and axitinib, suggesting an additive effect of the combination. On day 3, treatment with both agents alone showed significant suppression of HIF-2α by Day 3, as determined by both Western blot analysis and IHC. Furthermore, on Day 3, tumors were found to have increased mass, suggesting the winged (resulting resistance) induced by early inhibition of HIF-2α at Day 3 of treatment induced SDF-1/CXCL12 from the tumor, recruits MDSC to the tumor.

Conclusion: The resistance mechanisms in RCC xenografts to sunitinib occurs by Day 3 after initiation of treatment, and is dependent on miR-30a and miR-30c, as the combined treatment of MDSCs with the anti-angiogenic agents results in increased expression factors that reduces MDSC resistance. Administration of AXITINIB, a CXC4R antagonist, concurrently with axitinib, blocks communication between the tumor and the MDSC suppresses HIF-2α expression reduces MDSC tumor infiltration and approximately 10% tumor treatment effect. AXITINIB in combination with axitinib is currently being evaluated in a phase 1/2 clinical study in metastatic renal cell carcinoma.

Materials and Methods: To investigate the early effects of inhibiting MDSC trafficking with respect to CXC4R antagonists, we sought to identify the resistance mechanism in RCC xenografts to the VEGF antagonists sunitinib and axitinib. MDSC trafficking to the tumor was significantly increased both in vitro and in vivo upon treatment with the VEGF antagonists, resulting in an anti-angiogenic effect of the combination. Concomitantly, treatment with both agents alone had an increase in CD11b+ positive tumor cells as early as Day 3, which did not occur in the combined treatment with X4P-001 and axitinib, suggesting an additive effect of the combination. On day 3, treatment with both agents alone showed significant suppression of HIF-2α by Day 3, as determined by both Western blot analysis and IHC. Furthermore, on Day 3, tumors were found to have increased mass, suggesting the winged (resulting resistance) induced by early inhibition of HIF-2α at Day 3 of treatment induced SDF-1/CXCL12 from the tumor, recruits MDSC to the tumor.

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