First evidence that the anti-malarial drug Artesunate inhibits invasion and in vivo metastasis in lung cancer by targeting essential extracellular proteases

Autor: Suhail Ahmed Kabeer Rasheed
Institut / Klinik: Abteilung für Experimentelle Chirurgie und Molekulare Onkologie Solider Tumoren
Doktormutter: Prof. Dr. H. Allgayer

Despite progress in treatment, progressive non-small cell lung cancer (NSCLC) still limits survival dramatically, and novel therapeutic compounds are needed. Initial investigations suggest that Artesunate (ART), an anti-malaria drug, has anti-proliferative capacities. However, anti-invasive and anti-metastatic properties of ART in cancer have never been explored. In this thesis, we show that Artesunate is able to significantly impair matrigel invasion of cultured non-small cell lung cancer (a panel of 6 different NSCLC cell lines), and we show that this is paralleled by significant inhibition of the activity and expression of urokinase type plasminogen activator (u-PA), one of the most important and relevant invasion- and metastasis-related molecules in many solid cancer types. In addition, we conducted a systematic PCR-based metastasis array and found that ART inhibited the expression of several matrix metalloproteinases (MMPs), among them especially being MMP-2 and MMP-7. Both MMPs have also been implicated as decisive molecules of metastasis in diverse solid cancer types. We furthermore show that the downregulation of u-PA, MMP-2 and MMP-7 is being brought about at the transcriptional level, by inhibiting the respective promoters and/or upstream enhancer motifs that are decisive for transcriptional regulation of these genes. This is being paralleled by the ability of Artesunate to inhibit the transactivating capacity of AP-1 and NFkB transcription factors, which is also a finding that has not been shown in previous studies. In siRNA knockdown experiments, we demonstrate that the presence of u-PA, MMP-2 and MMP-7 not only is decisive for the ability of NSCLC cells to invade, but especially for the ability of Artesunate to inhibit NSCLC invasion, confirming the role of these three metastasis-related molecules as essential mediators of the anti-invasive action of ART. Moreover, in diverse in vivo experiments, we show that ART significantly downregulates the growth of primary tumors, and independently of this, in vivo metastasis in the chorion-allantoic membrane (CAM) metastasis model of the chicken embryo. Taken together, this is the first study to demonstrate that Artesunate considerably suppresses...
invasion and in vivo metastasis in non-small cell lung cancer, this specifically being brought about by the downregulation of transcription of u-PA, MMP-2 and MMP-7, as well as by inhibiting AP-1 and NFkB. These results, together with the notion that Artesunate already is clinically applied to human patients in the context of malaria treatment, should prompt rapid clinical studies on Artesunate as a novel therapeutic in NSCLC, and putatively also in other cancers, in which similar mechanisms need to be explored in future studies.