Guanine nucleotide exchange factor-H1 signaling is critical for induction of anti-tumor immunity induced by microtubule-depolymerizing drugs

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Apart from tumor cytotoxicity, chemotherapy can modulate the tumor microenvironment to promote anti-tumor immunity. We have shown that contrary to microtubule stabilizing agents (MSA) tubulin de-polymerizing agents (MDA) such as plinabulin (currently in Phase 3 in NSCLC), auristatins and maytansinoids reprogram the tumor immune environment by activating DCs and priming anti-tumour T cells. Furthermore, MDAs were shown in pre-clinical models to boost the activity of T cell immune checkpoint inhibitors such as PD1 and CTLA4. The mechanism behind MDA-induced DC activation remains unaddressed and was the focus of this study. We provide data suggesting that DC activation induced by MDAs is independent of pattern-recognition receptors, but is dependent on the engagement of the tubulin-associated protein, GEFH1 (guanine nucleotide exchange factor-H1). More specifically, MDAs stimulated the release of GEFH1 from microtubules leading to its activation and production of Rho-GTP. This was followed by the specific activation of MKK4, JNK and cJun, which remained inactive in GEFH1$^{-/-}$ DCs or DCs treated with the MSA paclitaxel. In contrast to wild type DCs, MDAs such as plinabulin were unable to activate GEFH1$^{-/-}$ DCs. More importantly, GEFH1$^{-/-}$ DCs treated with MDAs failed to prime antigen-specific CD8^{+} T cells compared to wild type DCs. Together, GEFH1 triggers a cascade of events that ultimately leads to the up-regulation of DC activation markers, pro-inflammatory cytokines, and T cell priming. Identifying the immunomodulatory properties of plinabulin and other MDAs has relevant clinical implications to maximize their therapeutic activity and to design their rational combination with immunotherapeutics such as PD1/PD-L1 directed therapies.