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## Hijacked senescence secretomes as 'immune primers' of antiangiogenic TKI efficacy

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# Investigating hijacked senescence secretomes as 'immune primers' following antiangiogenic TKI resistance

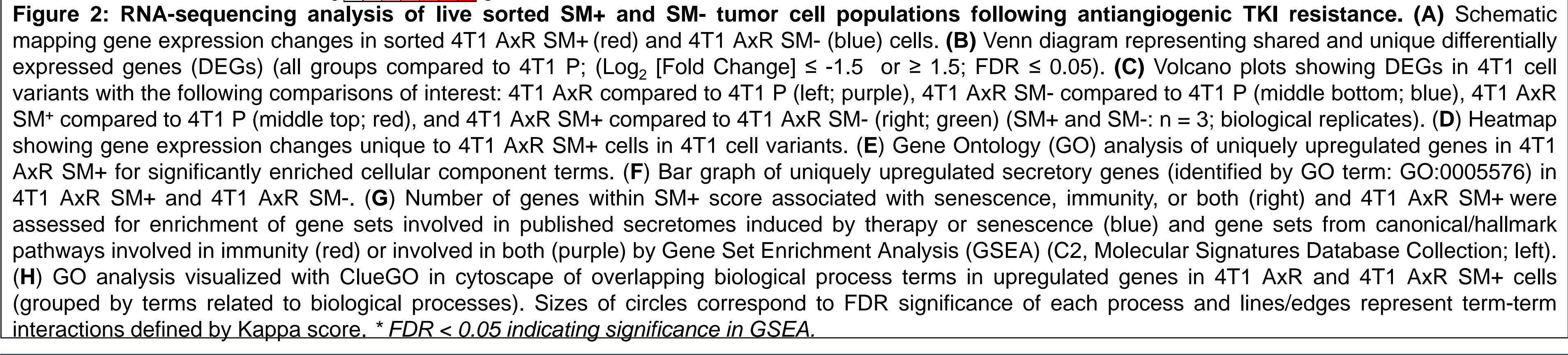
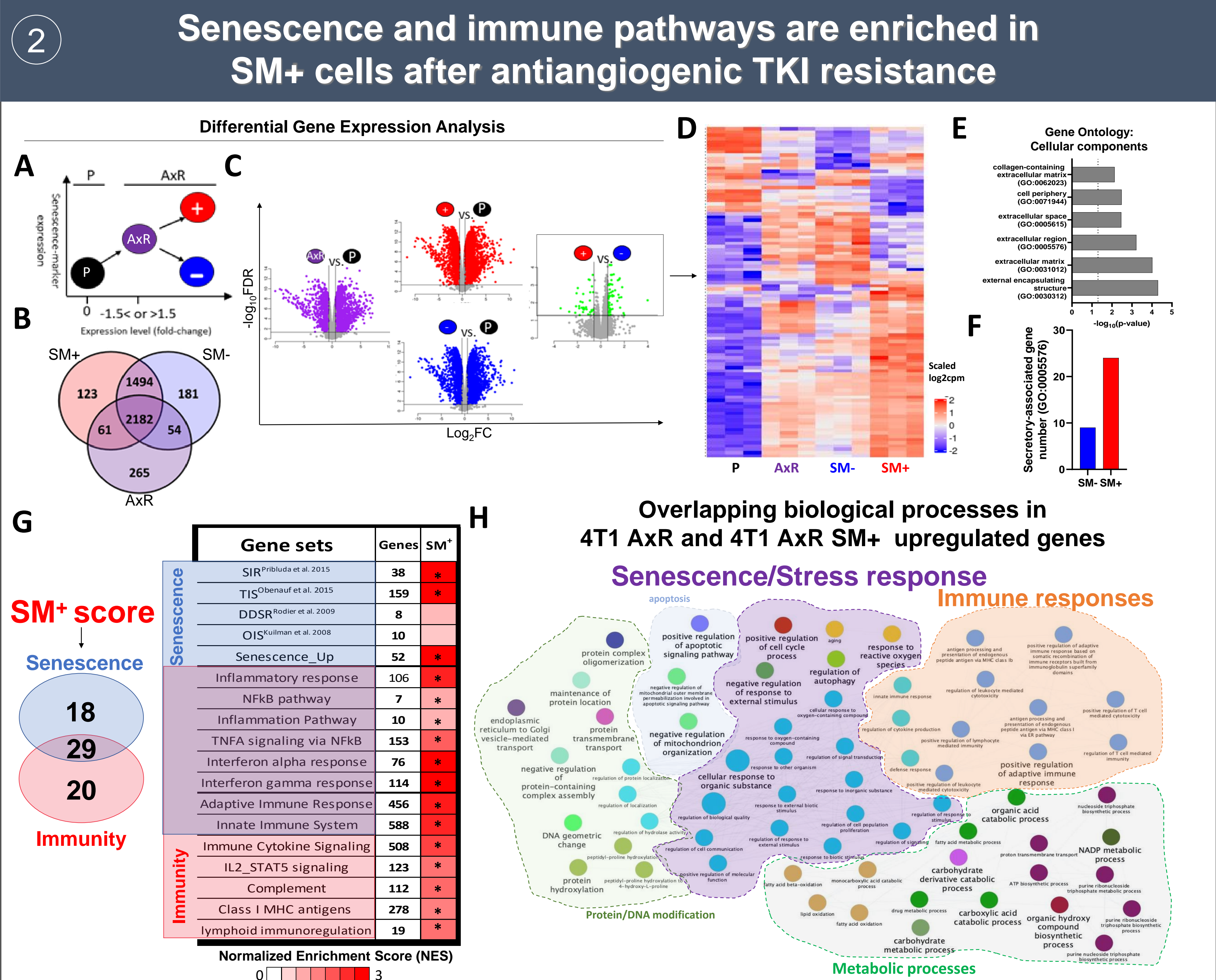
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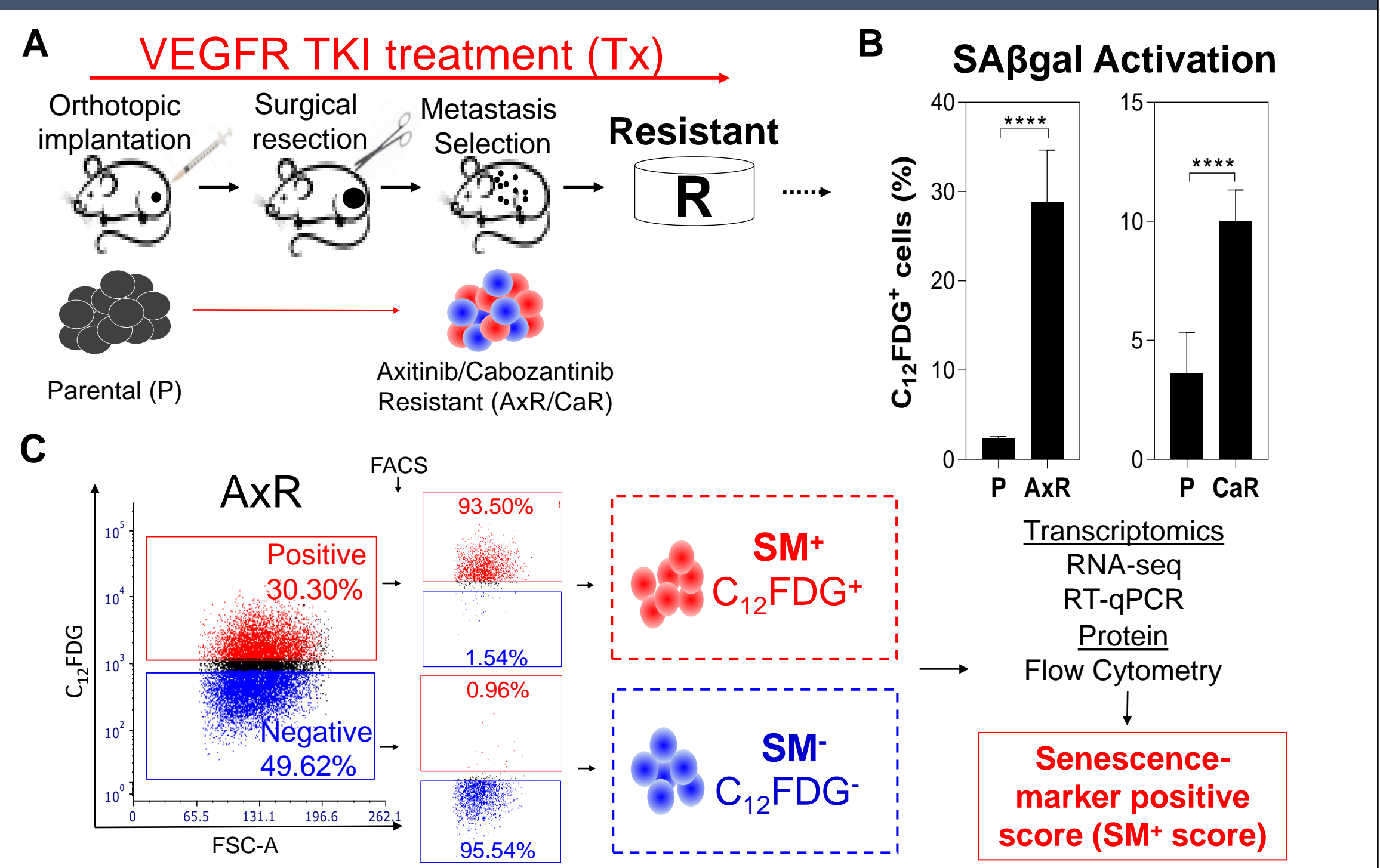


## Abstract

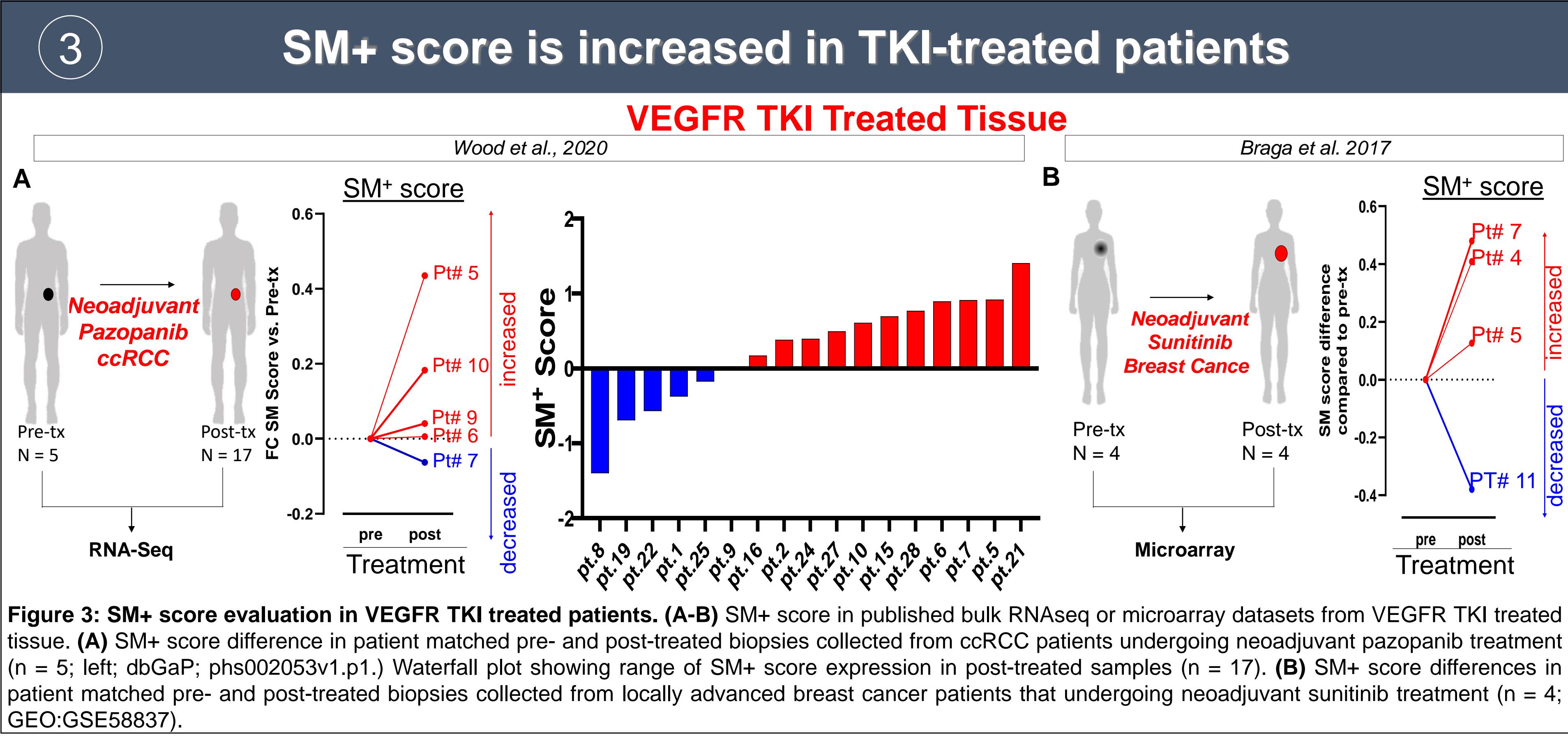
VEGF receptor tyrosine kinase inhibitors (VEGFR TKIs) and immune checkpoint inhibitors (ICIs) are approved together as a treatment regimen for multiple metastatic cancers, yet the mechanistic basis for this combinatory benefit remains unclear. Previously we have shown that resistance to VEGFR TKI treatment can transiently hijack the secretory machinery typically associated with senescence - the process of cellular aging. Here we report that these senescence-associated secretory programs can also drive immune cell activation, potentially 'priming' the tumor for PD-1 pathway inhibition. Using a novel live-cell sorting method based on C<sub>12</sub>FDG - a substrate for senescence-associated beta-galactosidase activity - we isolated senescence-marker (SM) expressing VEGFR TKI-treated cells for transcriptomic analysis. SM+ cell populations were enriched for senescence, immune, and interferon secretory processes, with a unique gene signature validated using published preclinical and clinical datasets. Notably, SM+ cells were found to be more sensitive to CD8 T-cell mediated tumor inhibition *in vivo* and *ex vivo* and be sensitive to PD-L1 blockade. Together, these results suggest VEGFR TKI controlled secretory programs contributing to resistance can simultaneously prime the tumor microenvironment for immune cell activation, providing an explanation for improved effects of antiangiogenic and immunotherapy combinations or treatment sequences in patients.



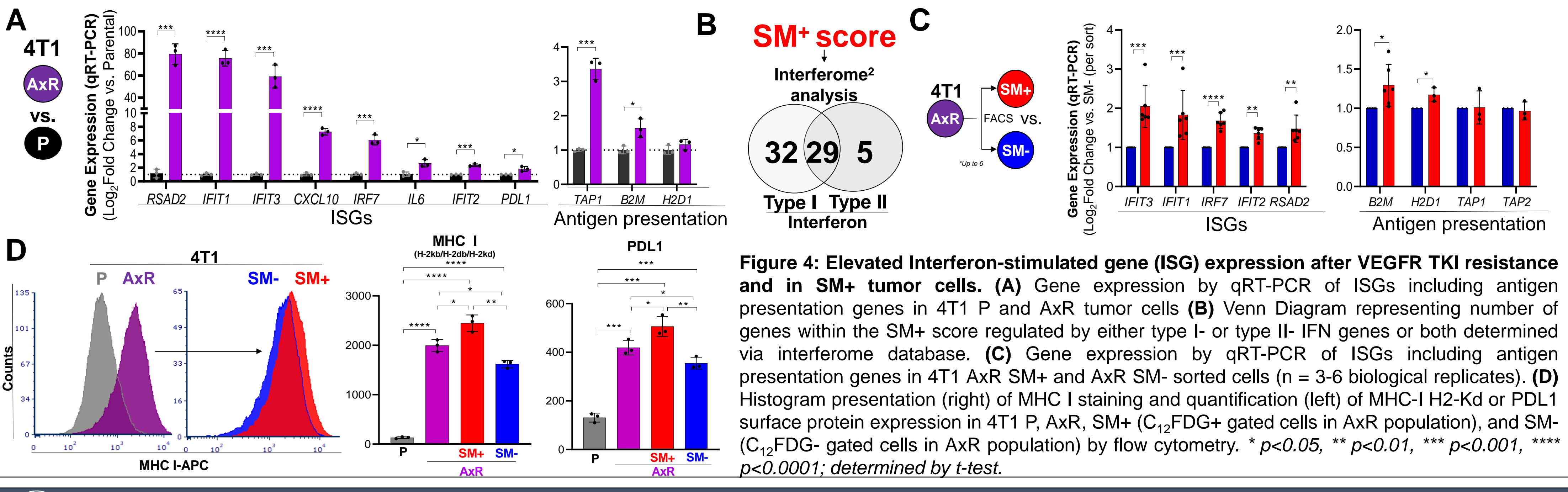
## 1 Isolation of live Senescence-marker (SM) cells following antiangiogenic TKI resistance



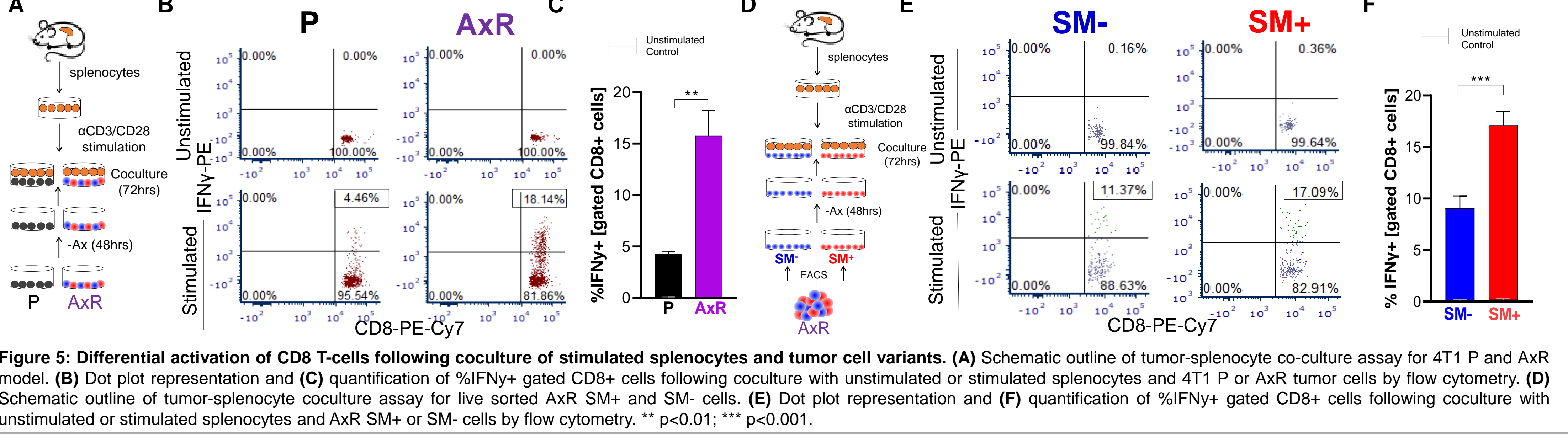
<sup>1</sup> Mastroi, M., et al. (2018). A Transient Pseudosenescent Secretome Promotes Tumor Growth after Antiangiogenic Therapy Withdrawal. Cell Reports 25(13):3706-3720.e8



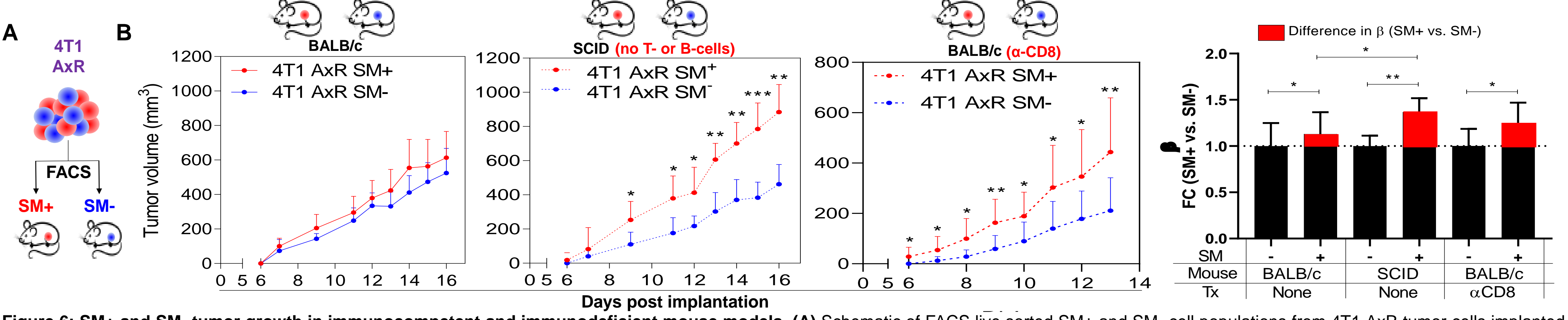
## 4 SM+ cells are enriched for IFN regulated genes including MHC I and PDL1



## 5 SM+ cells promote activation of stimulated CD8 T-cells



## 6 SM+ tumors are more sensitive to adaptive immunity



## 7 SM+ tumors are more sensitive to PDL1 inhibition

