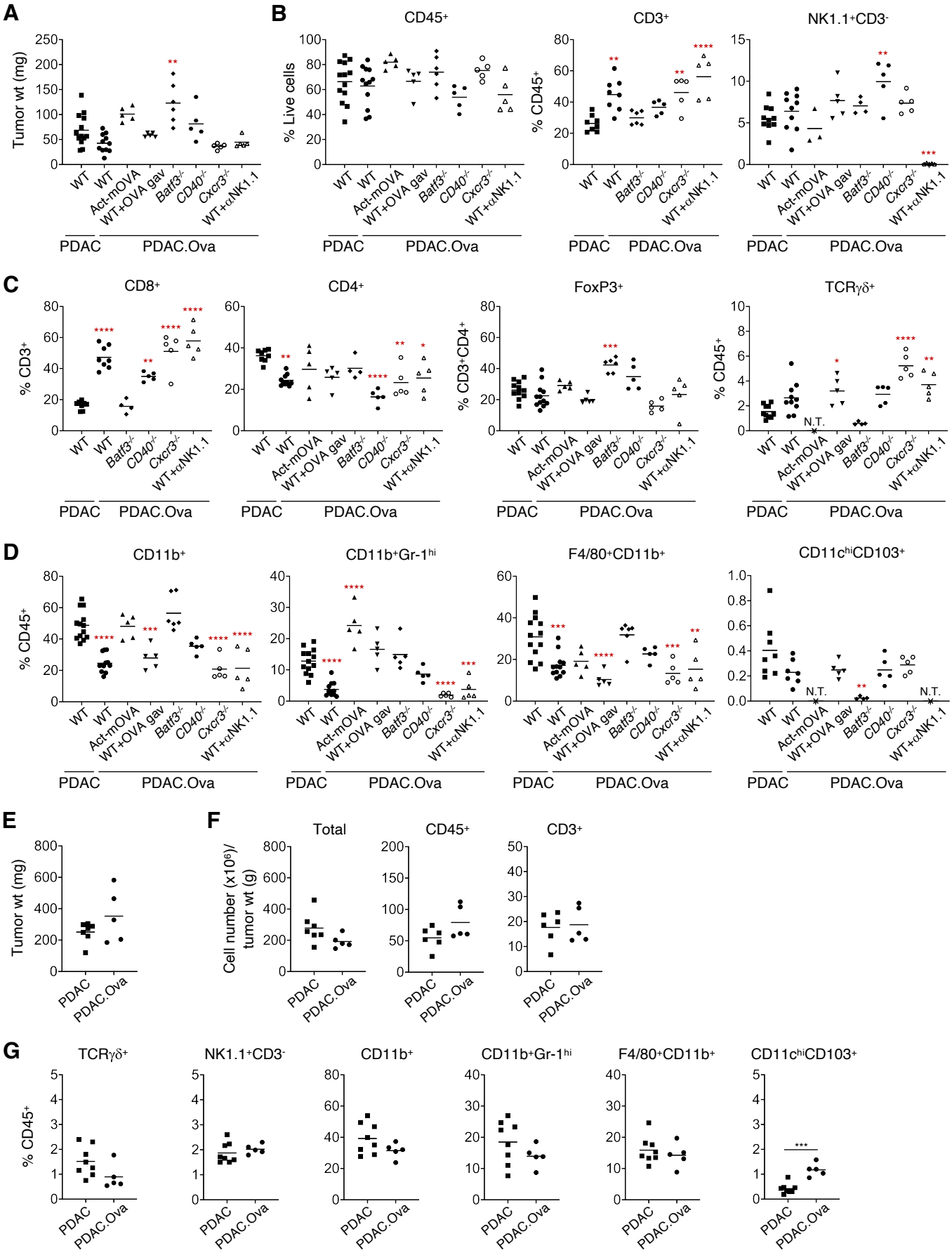**Supplementary Fig. S3**