Tumor cell-induced platelet aggregation is independent of tumor invasiveness as observed from both cell lines and primary tumors

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Background - Platelets & Metastasis

1. Platelets play a key role in the metastatic dissemination of tumor cells, by binding and protecting the invading tumor cells from shear stress and host immune system, creating a permissive microenvironment [1,2].
2. Platelet and tumor cell binding initiates platelet activation leading to the secretion of bioactive molecules, which promotes extravasation and metastasis [3].
3. Historically, cancer patients with elevated platelets have shown a higher incidence of metastasis [4].
4. Cancer-associated thrombosis is a major cause of mortality in cancer patients, after metastasis, with an increased risk in malignant tumors. Platelet activation, both direct and indirect, plays a key role in all such cases [5].

Method

1. Blood was collected from consented eight healthy volunteers (D1-8), who were not on any medicines for at least the last 30 days.
2. Platelet-rich plasma (PRP) and platelet-poor plasma (PPP, as control) were isolated as per modifications of standard protocols [6].
3. Tumor cells were added to the platelet-rich plasma and the aggregation of platelets induced by tumor cells was measured at an absorbance of 650nM in a kinetic mode for 60 min at a temperature of 37°C.

Results

Fig. 1: Standardization of platelet aggregation with ADP

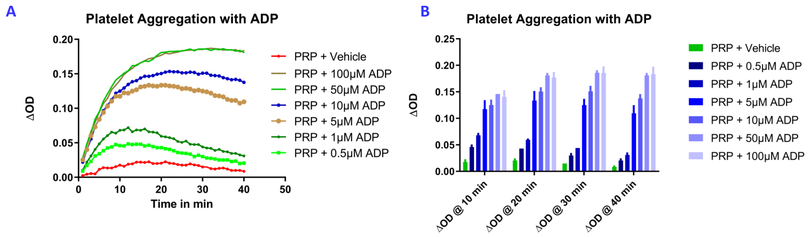


Fig. 2: Triple-negative breast cancer cell lines are more aggressive than colorectal cancer cell lines

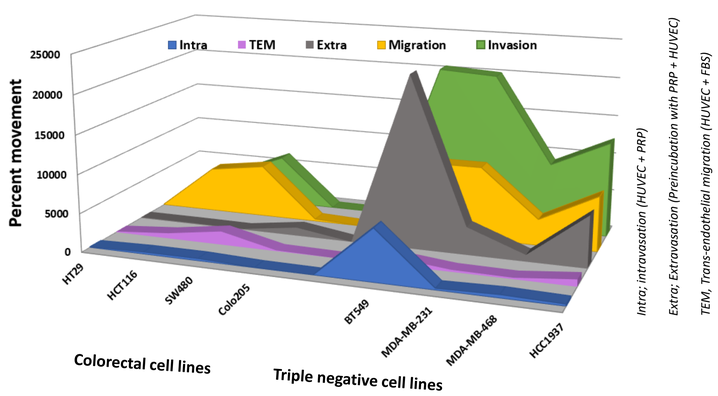
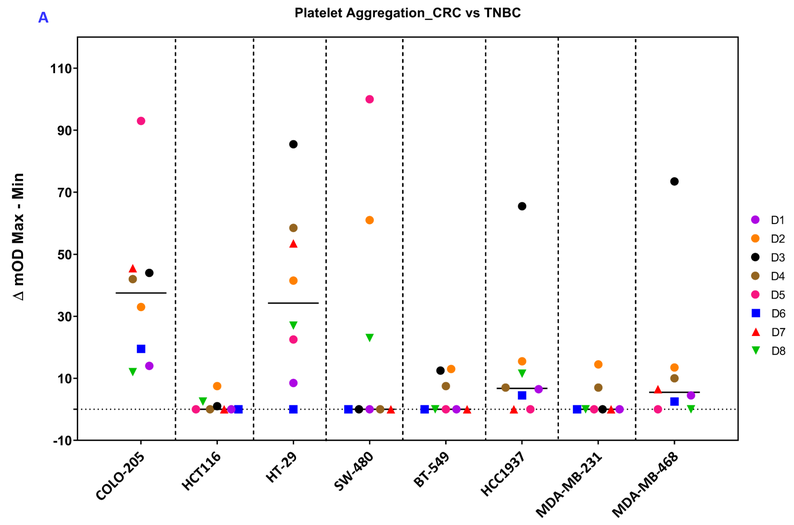
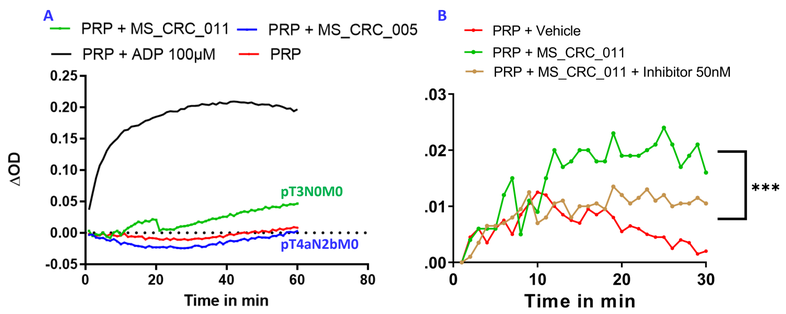


Fig. 3: Less Invasive colorectal cells show more platelet binding



1. Increased platelet activation with CRC, compared to TNBC is statistically significant across 8 volunteers and eight cell lines (3B).
2. Different platelets behave differently with the same cell lines (e.g Colo205 in 3A)
3. In the CRC cohort, less invasive HT29 showed more platelet activation than the aggressive HCT116 (3A).
4. In the TNBC cohort, non-metastatic MDA-MB-468 showed more platelet aggregation than with metastatic BT549 (3A).

Fig. 6: Node negative (N0) treatment naïve patient sample# shows comparatively greater aggregation than node-positive (N2b) patient sample



Tumor-platelet Interaction In Patients Can Be A Plausible Target To Delay Metastasis

Fig. 4: TNBC platelet activation follows a lag phase (B & D), suggesting an indirect pathway

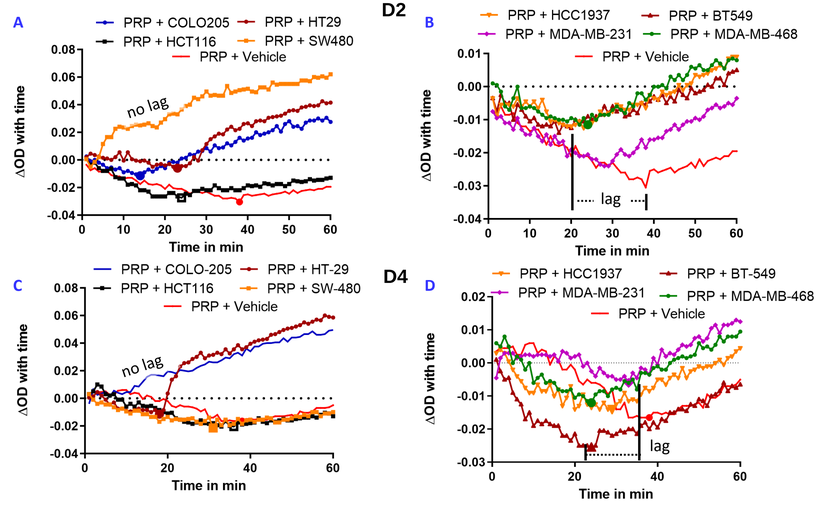
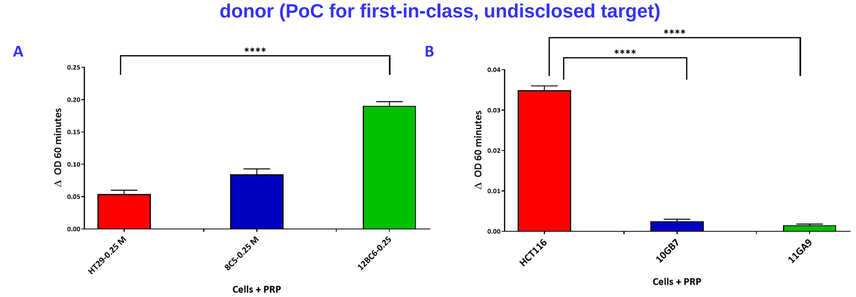


Fig. 5: Genetic conversion of noninvasive HT29 to invasive form increases aggregation (A) & conversion of invasive HCT116 to non-invasive form decreases aggregation (B) for the same donor (PoC for first-in-class, undisclosed target)



Summary

- Tumor and platelet interaction does not depend on tumor invasiveness (Fig 2,3 & 4).
- Individual patient platelet, associated microenvironment, and physiology play a determining role (Fig 3).
- The tumor platelet interaction can be altered by controlling the genetic expression of a first-in-class target (undisclosed) (Fig. 5).
- A tool compound for this first-in-class target (undisclosed) shows initial proof-of-concept (Fig. 6).

References

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#All patient samples were Tumor Review Board and Ethics Committee approved