Ovarian cancer's protective barrier: How the tumor matrix teaches cells to disarm immune attack

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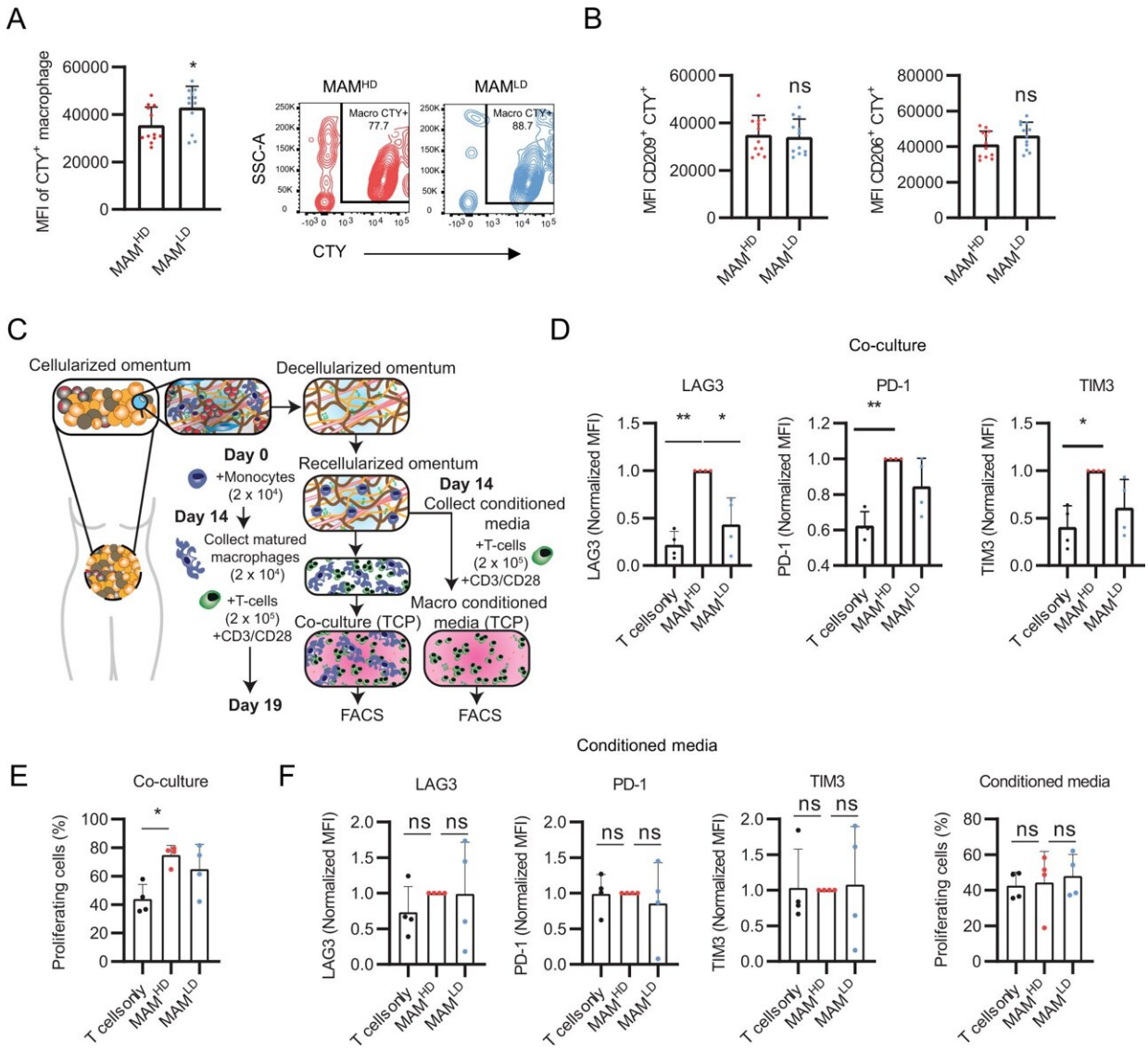

HD MAMs have a reduced phagocytic response and alter T cell activation in the presence of CD3 and CD28 stimulation. MAMs were cultured for 14 days and K562 cells were cultured for 5 days prior to use in phagocytosis assay. Cell types were mixed for phagocytosis assay. A Flow cytometry analysis of mean fluorescence intensity (MFI) of HD (MAM^{HD}) and LD MAMs (MAM^{LD}). Data are presented as mean values +/− SD. p = 0.02. Two-tailed Mann-Whitney U test used. Representative contour plots of CTY^+ macrophages cultured between HD and LD ECM. N = 4 LD MAM or HD MAM samples, with 3 technical repeats per sample. B MFI of $CD209^+$ and $CD206^+$ CTY^+ cells. Data are presented as mean values +/− SD. Two-tailed unpaired T-test used. p = 0.77, p = 0.11, respectively. N = 4 LD MAM or HD MAM samples, with 3 technical repeats per sample. C Schematic of MAMs and T cell co-culture workflow. Flow gating strategy provided in Supplementary Fig. 24. D Normalized MFI of LAG3, PD1 and TIM3 expression on $CD3^+$ T cells as assessed using flow cytometry after 5 days culture alone or co-culture with HD or LD MAMs. Data are presented as mean values +/− SD. One-way ANOVA followed by Dunnett's multiple comparisons test. LAG3 **p = 0.0026, *p = 0.0444, PD-1 **p = 0.0039, TIM3 *p = 0.0209, N = 4. E Percentage of proliferating $CD3^+$ T cells as assessed by Cell Trace Violet dilution using flow cytometry after 5 days culture alone or co-culture with high or low disease MAMs. Data are presented as mean values +/− SD. One-way ANOVA followed by Dunnett's multiple comparisons test. *p = 0.013, N = 4. F Normalized MFI of LAG3, PD-1, and TIM3 expression on $CD3^+$ T cells and percentage of proliferating $CD3^+$ T cells as assessed using flow cytometry after 5 days culture alone or co-culture with high or low disease MAMs conditioned media. Data are presented as mean values +/− SD. One-way ANOVA followed by Dunnett's multiple comparisons test. N = 4. Credit: *Nature Communications* (2023). DOI: 10.1038/s41467-023-38093-5

A structure surrounding ovarian cancer trains cells called macrophages to protect the tumor from immune attack, according to new research led by Queen Mary University of London.

The work uncovers tactics that the tumor uses to disarm the immune system and points toward potential therapeutic strategies to overcome

the cancer's defenses and treat patients more effectively.

The extracellular matrix is a network of scaffolding that surrounds our cells and helps to maintain the 3D shape and structure of our tissues. Tumors manipulate and rearrange this structure as they develop to support their growth and spread. However, new research shows that the matrix is not merely an inert skeleton, but a dynamic and active accomplice in tumor development.

Dr. Oliver Pearce, lead co-author and Lecturer at Queen Mary's Barts Cancer Institute, says, "The matrix was previously seen as a bystander in this process, but recently, people have realized that it has a direct functional effect on how tumors develop and, most importantly, how tumors are likely to respond to treatment."

The matrix provides a line of defense around tumors that excludes and disarms immune cells, blocking them from attacking the cancer. This can cause potentially potent immunotherapies to fail, as their ability to boost the immune system's power to fight cancer is rendered useless if immune cells cannot infiltrate the tumor.

"We wanted to find out: what are the important components of the matrix that suppress the immune system?" explains Dr. Eleanor Tyler, postdoctoral researcher in Dr. Pearce's lab and lead co-author, "and can we target these to improve immune infiltration and the efficacy of therapies?"

In the new study, published in *Nature Communications*, Dr. Tyler analyzed data from tumor samples from 12 different types of cancer, including ovarian cancer. She found that patients' disease progressed more rapidly when the matrix around their tumor contained a set of five key molecular building blocks. Interestingly, matrix built this way often contained cells called M0 macrophages, a mysterious class of immune

cells that remains poorly understood.

This raised questions: Are these cells helping to suppress an immune response and protect the tumor? And why are these macrophages so abundant in matrix containing these five molecules?

The researchers speculated that the tumor matrix could be operating like a school, training immature immune cells to become M0 macrophages. To test this theory, they took samples of ovarian tumors and stripped away all of the cells, leaving behind the architecture of the matrix, fully intact.

Next, the team introduced immature cells called monocytes into this structure. "To our surprise, the monocytes we put into this model matured into macrophages similar to the M0 cells we saw in human tumor tissues without any other stimulus. The matrix instigates this change by itself," Dr. Pearce comments.

In collaboration with colleagues at the University of Basel, Switzerland, the researchers also revealed that their M0 macrophages can suppress components of the immune response—such as T cells, which play an important role in tumor killing. T cells incubated with these macrophages did not proliferate as quickly and showed signs of being deactivated.

These results could pave the way for new drugs that target parts of the matrix and disrupt its ability to suppress immune responses to the tumor. Dr. Pearce and his team are already working with biotech companies to develop potential therapies that target aspects of the matrix and lower the tumor's defenses. These approaches could be used in combination with immunotherapies to boost their efficacy and improve patients' survival.

More information: E. H. Puttock et al, Extracellular matrix educates an immunoregulatory tumor macrophage phenotype found in ovarian cancer metastasis, *Nature Communications* (2023). DOI: 10.1038/s41467-023-38093-5