Umor-Associated Macrophage Subtypes are Associated with Distinct Clinical Phenotypes in Nonfunctional Pituitary Adenoma

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Introduction

Tumor-associated macrophages (TAMs) contrubute to tumor growth and invasiveness, with transcriptional profiling suggesting M1 and M2 subtypes with anti-tumoral and pro-tumoral effects, respectively. There is little research on TAMs and their subtypes in nonfunctional pituitary adenomas (NFPAs).

Methods

NFPA cell suspensions underwent FACS for CD11b+ TAM isolation. M1 (CXCL10, IL1B) and M2 (ARG1, MMP9, TGFb) marker qPCR yielded an M2/M1 gene expression ratio. The THP1 human monocyte cell line was polarized into M1 versus M2 macrophages by incubating with IFN-? or IL-4, respectively, with primary NFPAs incubated in conditioned media (CM) from macrophages to assess biologic effects.

Results

FACS revealed TAMs to comprise 7.9% of total NFPA cells (range 0.5%-28.1%), displaying a bimodal distribution with most cases clustering at a low (<12%) TAM fraction, but two cases exhibiting elevated 18-28% TAM fractions. These TAM-rich NFPAs were the most expansile tumors (size > 3.5 cm or MIB1>3%). qPCR revealed M2/M1 gene expression ratios to also be bimodal, with the high M2/M1 ratio group (range=4.3-2.1X107) all exhibiting cavernous sinus invasion and no cases with low M2/M1 ratio (range=3.6X10-7-2.7) exhibiting cavernous sinus invasion. Increasing TAM fraction was associated with decreased M2/M1 ratio. CM from M2 macrophages increased proliferation ($P<10^{-4}$) and invasion ($P<0.01$) of cultured NFPA cells more than CM from M1 macrophages. Increased expression of invasion promoting genes S100A8 and S100A9 was seen in NFPA cells grown in CM from M2 vs. M1 macrophages.

Conclusions

TAMs distinguished two NFPA groups: Group 1 exhibited high TAM levels with a more M1 TAM profile and were larger, more proliferative, less invasive adenomas; while Group 2 exhibited low TAM levels with a more M2 profile and were smaller, more invasive adenomas. These findings suggest that different NFPA groups are driven by distinct TAM subtypes. Analyses like this could produce immunomodulatory therapeutic approaches for NFPAs.

Learning Objectives

By the end of this session, participants should be able to 1) describe the macrophage subtypes surrounding nonfunctional adenomas, and 2) their association with different clinical characteristics of adenomas including size and invasiveness.

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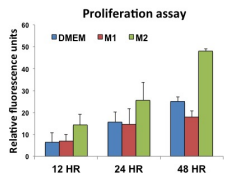
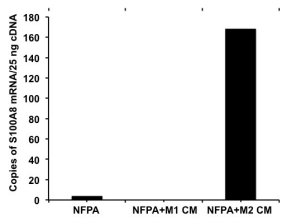
Figure 1



Graph demonstrating increased proliferation (measured in relative fluorescence units, y-axis) over time (x-axis) among nonfunctional pituitary adenoma cells cultured in M2 macrophage conditioned media (green bars) versus M1 macrophage conditioned media (red bars) and negative control DMEM (blue bars).

Figure 2



Increased expression of invasion promoting gene S100A8 (y-axis) was seen in nonfunctional pituitary adenoma (NFPA) cells grown in M2 macrophage conditioned media (CM) versus M1 macrophage conditioned media (CM) (x-axis).