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Conceptual Analogies Between Multi-Scale Feeding and Feedback Cycles in Supermassive Black Hole and Cancer Environments

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Adopting three physically-motivated scales ("micro" – "meso" – "macro", which refer to mpc – kpc – Mpc, respectively) is paramount for achieving a unified theory of multiphase active galactic nuclei feeding and feedback, and it represents a keystone for astrophysical simulations and observations in the upcoming years. In order to promote this multi-scale idea, we have decided to adopt an interdisciplinary approach, exploring the possible conceptual similarities between supermassive black hole feeding and feedback cycles and the dynamics occurring in human cancer microenvironment.

Keywords: cancer microenvironment, exosomes, metastasis, multi-scale feeding and feedback cycles, supermassive black holes

INTRODUCTION

Several scientific problems show complexities that can be understood only through a multi-scale approach, in which apparently disjointed processes are linked together across multiple scales. One of such examples is the astrophysical study of supermassive black holes (SMBHs), which resides at the core of virtually every galaxy in the universe. Feeding of matter from galactic distances onto SMBHs is thought to be the physical process powering active galactic nuclei (AGN), which are observed up to extremely large distances due to their large luminosities and are supposed to impact the evolution of their host galaxies through mechanical feedback from winds and jets (1–3).

It is important to remind that the typical scale associated with a SMBH is in units of its Schwarzschild radius $rs = 2GM_{BH}/c^2$, where G is the gravitational constant, c is the speed of light, and M_{BH} is the mass of the SMBH. For a value of the SMBH mass of $\simeq 10^{10}$ times that of our Sun, this corresponds to a scale in units of parsec of 1 mpc $= 10^{-3} pc \simeq 10^{14} \circ cm$. This scale is larger than the distance between our Earth and the Sun, but it is negligible when compared to the size of a typical galaxy that can span a radius of more than 10 kpc. Therefore, the study of AGN and their host galaxies is inherently a multi-scale problem.

It has been recently assessed that adopting three physically-motivated scales ("micro" – "meso –macro, which refer tompc – kpc – Mpc, respectively) is paramount for achieving a unified theory of multiphase AGN feeding and feedback, and it represents keystone for astrophysical simulations and observations in the upcoming years (4). In order to promote this multi-scale idea, we have decided to adopt an interdisciplinary approach, exploring the possible conceptual similarities between SMBH feeding and feedback cycles and the dynamics occurring in human cancer microenvironment.

To this end, analogously to the three major scales ("micro", "meso" and "macro") identified in the aforementioned astrophysical investigation, we defined three distinct scales within the tumor microenvironment: (1) micro ≡intratumor network; (2) meso≡ intercellular exchanges between tumor and immune cells; and (3) macro ≡extracellular vesicles-based communication between primary tumor and distant pre-metastatic niches. In these three contexts, cell-to-cell communication is mediated by exosomes, nano-sized vesicles (40-100 nm in diameter) enclosed by a lipid bilayer and released by cells under healthy or pathological conditions (5) (**Figure 1**). Exosomes contain a variety of biomolecules that include oncogenic proteins, signaling molecules, glycans, lipids, metabolites, RNA, and DNA (6).

MICRO: EXOSOME-BASED INTRATUMOR COMMUNICATION

Studies focused on a variety of distinct cancer cells reported that tumor-derived exosomes can promote tumor cell proliferation. An autocrine induction of cellular proliferation was reported in chronic myeloid leukemia (7), gastric cancer (8), bladder cancer (9), glioblastoma (10) and melanoma (11). Furthermore, exosomes-based intratumor communication is also fundamental for the acquisition of migratory properties in

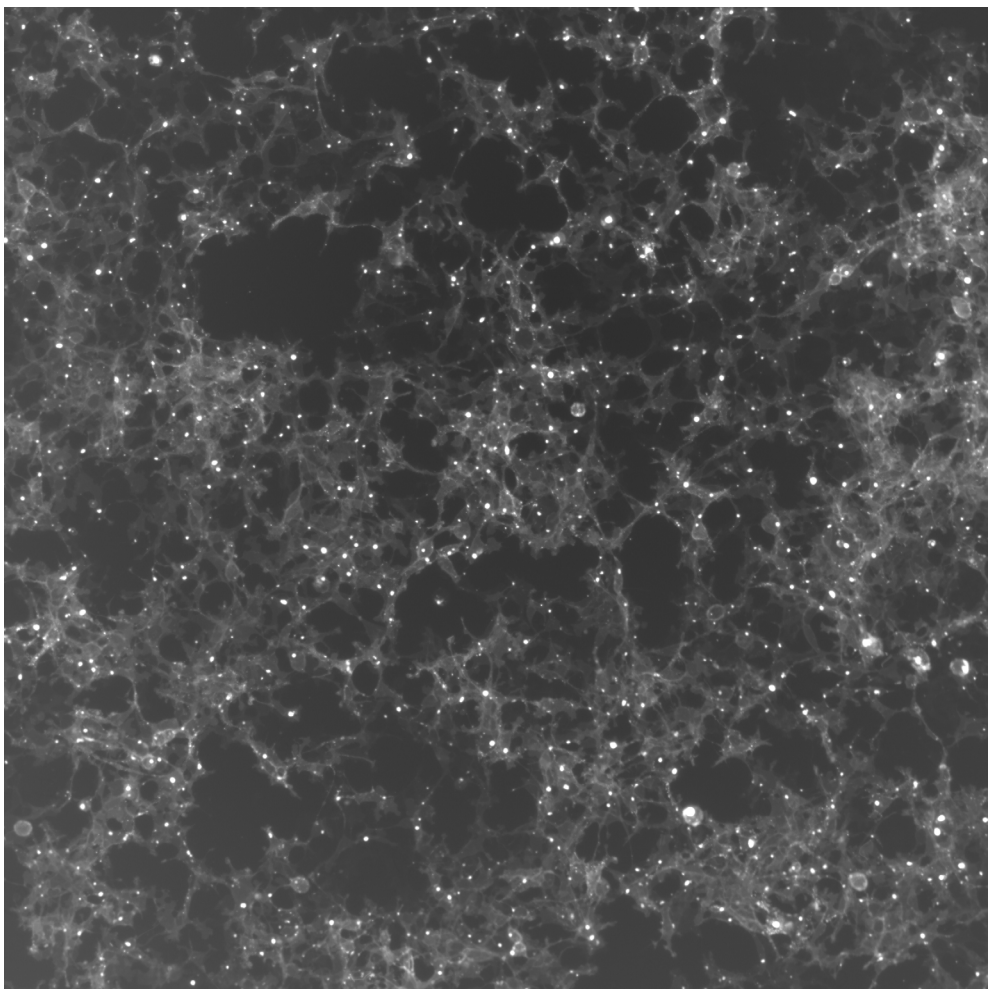

FIGURE 1 | Fluorescence image of HEK293T cells in culture. The clear areas indicate a high concentration of exosomes. These cells were engineered to produce exosomes containing the GFP fluorescent protein.

cancer cells from the primary tumor. This phenomenon has been reported in both nasopharyngeal carcinoma (12) and prostate cancer (13), where exosomes released by primary tumor cells can increase the invasiveness and motility of other recipient malignant cells (**Figure 2**).

A single cancer cell can produce and release in the blood from 2000 to 7000 exosomes (14). In 2018, Professor Avner Friedman and Professor Wenrui Hao (15) developed a mathematical model that resumes the production of tumor exosomes and the release of their content upon encountering cancer cells:

$$\underbrace{\frac{\partial Ec}{\partial t}}_{production} \underbrace{-D_{Ec}\Delta E_c}_{degradation} = \lambda_{Ec}C - D_{Ec}E_c\left(\frac{C}{C+K_C}\right)$$

where E_c identifies the exosomes produced by cancer cell over time, t = time, $D_{Ec}$is the diffusion coefficient of E_C, λ_{Ec} is the production rate of E_c, C means Cancer cell density and Kc indicates cancer cell saturation.

Exosomes released by tumor cells provide a paracrine signaling mechanism for cancer progression. Exosomes contain microRNAs (miRNAs), lipids and proteins that are cell type specific. The secretion and delivery of exosomal miRNAs are the basis for cancer cell-to-cell communication and contribute as signaling molecules to the creation of a tumor-promoting environment (16). The transfer of exosomal miRNAs can confer also acquired drug resistance by encoding proteins that can lead to chemoresistance in the recipient tumor cells (17).

miR-21 is one of the most studied (18) and enhances tumor growth when is released by exosomes through the encounter between E_c and cancer cells, as expressed by the equation (15):

$$\frac{\partial miR21}{\partial t} - DmiR - 21\Delta_{miR21} = \underbrace{\lambda_{miR21Ec}Ec\frac{C}{C+Kc}}_{production} - \underbrace{d_{miR21}miR - 21}_{degradation}$$

where $D_{miR\text{-}21}$ is the diffusion coefficient of miR21once released by exosomes, estimated at 0.130 cm^2/day (19), $\lambda_{miR21Ec}$ represents the production rate of miR-21 by Ec, Kc indicates cancer cell saturation (estimated at 0.4 g/cm^3) (20) and $d_{miR21}$the degradation rate of miR-21.

MESO: EXOSOME-BASED DIALOGUE BETWEEN TUMOR AND IMMUNE CELLS

The ability to develop strategies to escape from host immune surveillance is one of the hallmarks of cancer (21). It has been shown that tumor-derived exosomes can down-regulate CD3ζ and Janus kinase 3 (JAK3) expression in primary activated T-cells, mediate the apoptosis of $CD8^+$ T-cells and the conversion of $CD4^+$ $CD25^-$ T-cell into $CD4^+CD25(hi)FOXP3^+$regulatory T-cells, (which express interleukin 10, transforming growth

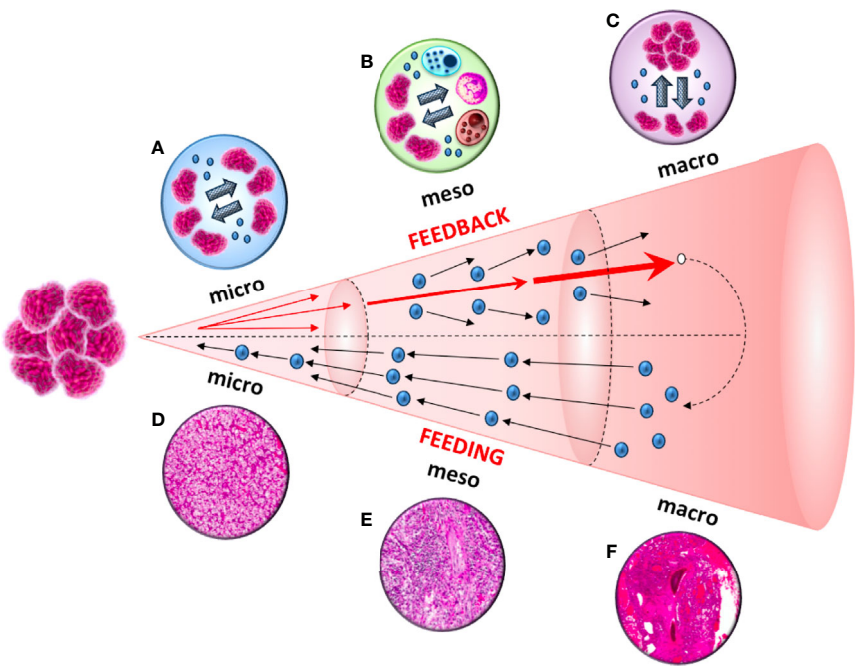

FIGURE 2 | A diagram of the feeding and feedback cycles, showing the geometric increase of three orders of magnitude (micro, meso and macro) in tumor microenvironment. Tumor-derived exosomes can increase the invasiveness and motility of recipient cells. This exosome-mediated communication occurs at three different levels: between cancer cells in the primary tumor (micro), between cancer and immune cells (meso) and between cancer cells from the primary tumor to the metastatic sites (macro).

factor β1 and cytotoxic T-lymphocyte antigen 4 that effectively mediate suppression) (22) (**Figure 2**).

E_c produced by tumor cells release their content through the encounter with a variety of immune cells including Th1 cells *(T_4)*, CD8+ cells *(T_8)*, regulatory T cells *(T_r)* and dendritic cells *(D)*:

$$\underbrace{\lambda_{Ec}\, C}_{production} - \underbrace{d_{Ec}E_c\left(\frac{T_4}{T_4+K_{T4}}+\frac{T_8}{T_8+K_{T8}}+\frac{T_r}{T_r+K_{Tr}}+\frac{D}{D+K_D}\right)}_{degradation}$$

where T_4, T_8, T_r and D express different immune cell density, while K indicate cell saturation estimated at 2 x 10^{-3} g/ml for T_4 and T_8, 5 x 10^{-4} g/ml for T_r (20, 23) and 4 x 10^{-6} g/cm^3 for D (24–26). The complex interactions of T_8,D and tumor cells *(T)* within the tumor has been described by Depillis and colleagues (27), who extended the model previously elaborated by Ludewig *et al.* (28) by adding a tumor compartment. In particular, they took into account tumor-immune system parameters such as immune cell trafficking rates to and from the tumor, effector cell deactivation rates by tumor cells, effector cell death rates, intrinsic tumor growth rates, and tumor cell kill rates by effector cells (27). The interactions of T_8,D and T were described by:

$$\underbrace{\frac{d}{dt}E^a_{tumor} = \mu_{BTE}(T)E^a_{blood} - a_{EaT}E^a_{tumor} - cE^a_{tumor}T}_{Interactions\ \ between\ \ CD8^+ and\ \ tumor\ \ cells}$$

where E^a_{tumor} is the number of CD8$^+$ cells within the tumor, T is the number of tumor cells, μ_{BTE} is the T-dependent rate at which effector cells enter the tumor compartment from the blood, E^a_{blood} is the number of CD8$^+$ cells in the blood, a_{EaT} is the death rate of activated CD8$^+$ in the tumor [estimated at 0.462/day (29)], c is the rate at which activated CD8$^+$ are inactivated by T [estimated at 9.42 x 10^{-12} cells x day (27)];

$$\underbrace{\frac{d}{dt}T = rT\left(1-\frac{T}{k}\right) - DT \cdots\cdots with\ \ D = d\frac{\left(\frac{E^a_{tumor}}{T}\right)^l}{s+\left(\frac{E^a_{tumor}}{T}\right)^l}}_{Tumor\ \ growth\ \ and\ \ lysis\ \ by\ \ CD8^+}$$

where r is the tumor growth rate [estimated at 0.3954/day (30)], k *is* the carrying capacity of tumor [estimated at 1.0 x 10^9 cells (30)] s is the value of $\frac{E^a_{tumor}}{T}$ necessary for half-maximal activated CD8$^+$ toxicity and l indicates the immune strength scaling exponent;

$$\underbrace{\frac{d}{dt}D_{tumor} = \frac{mT}{q+T} - (\mu_{TB}+a_D)D_{tumor}}_{Interations\ \ between\ \ tumor\ \ and\ \ dendritic\ \ cells}$$

where D_{tumor} is the number of tumor-infiltrating dendritic cells, m is the maximum recruitment rate of DCs to tumor site [estimated at 2.4388 x 10^4 cells/day (27)], q is the value of T necessary for half-maximal DC recruitment [estimated at 100 cells (27)], μ_{TB} is the rate of dendritic cell transfer from tumor to blood [estimated at 0.0011/day (27)], and a_D is the natural death rate of dendritic cells [0.2310/day (28)].

MACRO: EXOSOME-BASED COMMUNICATION BETWEEN PRIMARY TUMOR AND METASTASES

As reported above, tumor-derived exosomes promotes the invasiveness and motility of tumor cells from the primary site to metastatic niches (12, 13) (**Figure 2**). By analyzing different cell lines, Yu et al. (31) observed 79 proteins that were differently expressed in exosomes between more and less metastatic tumors, and these proteins were implicated in cell adhesion, invasion, growth, metabolism and metastasis (31). Tumor-derived exosomes are crucial for the formation of pre-metastatic niches (32), which are necessary for the creation of a suitable environment for circulating tumor cells (CTCs) colonization and growing within a secondary site (33). The choice of metastatic sites is orchestrated by the primary tumor through secreted factors, with exosomes representing the main extravescicular population that mediates long-range signaling during metastasis (34–36). Exosome proteomics revealed distinct integrin expression patterns that could be used to predict organ-specific metastasis (37). For example, exosomalintegrinsα6β4 and α6β1 were linked to lung metastases, while αvβ5 was associated to liver metastases (37), supporting the organotropism of tumor-derived exosomes.

If we assume that the production of tumor exosomes E_c and the release of their content upon encountering cancer cells can be described by:

$$\underbrace{\frac{\partial Ec}{\partial t} - D_{Ec}\Delta E_c = \lambda_{Ec}C - d_{Ec}E_c\left(\frac{C}{C+K_C}\right)}_{production\ \ degradation}[12]$$

We can derive that the diffusion of tumor-derived exosomes from primary tumor to pre-metastatic niches ($D_{Ec}\Delta E_c$) can be described by:

$$\underbrace{D_{Ec}\,\Delta E_c = \frac{\partial Ec}{\partial t} + d_{Ec}Ec\left(\frac{C}{C+K_C}\right) - \lambda_{Ec}C}_{Diffusion\ \ of\ \ exosomes\ \ from\ \ primary\ \ tumor\ \ to\ \ metastastic\ \ cells}$$

Where λ_{Ec} is the production rate of E_c and Kc indicates cancer cell saturation.

The diffusion of tumor-derived exosomes (D_{Ec}) from the primary tumor the pre-metastatic niche can be estimated through considering the average diameters of exosomes (70 nm) at1.23 x 10^{-4} cm^2/day (15). The release of E_c promotes the initial phases of tumor invasion and metastatization, described by the model we adapted from that proposed by Lai and Friedman (38):

$$\underbrace{\frac{\partial C}{\partial t} - D_c\Delta C - \chi\nabla(C\nabla C)}_{Tumor\ \ invasion} = \underbrace{(\lambda_{C1}\frac{SP_1}{K_{SP1}+SP_1} + \lambda_{C2}\frac{SP_2}{K_{SP2}+SP_2})C\left(1-\frac{C}{C_M}\right)}_{Tumor\ \ growth} - \underbrace{(d_DC + d_CC)}_{Tumor\ \ apoptosis}$$

where D_c is the diffusion coefficient of cancer cells, $\chi\nabla$ *(C* ∇*C)* indicates the migration of cancer cells, λ_C the growth rate due respectively to driver signalling pathways 1 (SP_1) and 2 (SP_2), C_M the carrying capacity of tumor cellsand d_DC *and* d_cC account, respectively, for the rate of damage-induced or natural apoptotic cancer cells.

CONCLUSIONS

Analogies between multi-scale feeding and feedback cycles in supermassive black hole and cancer environments can allow the crossover of mathematical models between these two fields. Nevertheless, our model should be validated. The recent advances in tissue biology on several spatial scales including multi-cellular, single cell and the sub-cellular levels will expand our comprehension of the mechanisms of exosome-mediated communication and will allow us to measure the distances needed for cell-to-cell interactions. In this context, Nanostring technology can be employed to investigate tumor spatial and time heterogeneity. The potential consequences of the creation and validation of this model on the exosome-mediated communication between tumor cells and immune cells will be both clinical and therapeutical. Indeed, modelling exosome-mediated communication may allow to predict the time to metastases, to avoid tumor-induced immunosuppression and to develop exosomes for targeted delivery drug.

A straight cooperation and merging of such apparently distant disciplines may result a turning point to exceed the current limits of astrophysical and oncological modelling procedures in future years.

AUTHOR CONTRIBUTIONS

MS: conceptualization and writing. FT: conceptualization and writing. AC: data collection. RM: supervision. FP: data collection and supervision. All authors contributed to the article and approved the submitted version.

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