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Baseballs, tennis balls, livestock farm manure, the IDH1 mutation, endothelial cell proliferation and hypoxic pseudopalisading (granulomatous) necrosis: *Mycobacterium avium* subspecies *paratuberculosis* and the epidemiology, cellular metabolism and histology of diffuse gliomas, including glioblastoma

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Abstract
An increased rate of diffuse gliomas, including glioblastoma, has been noted in livestock farmers in Western countries. Some researchers have suggested that a zoonotic virus or bacteria present in the livestock animal's feces or manure may be a possible etiologic factor. *Mycobacterium avium* subspecies *paratuberculosis* (MAP), the cause of a chronic enteropathy in domestic livestock and a probable zoonosis, is heavily excreted in an infected animal's feces or manure, contaminating soil and ground on the animal's farm. Once excreted in an animal's feces, MAP lasts indefinitely in a dormant but viable form, and easily spreads outside farms to the surrounding environment. MAP's presence throughout the soil in countries where MAP infection of domestic livestock is extensive and long-standing may explain the increased rates of glioblastoma in tennis and baseball players who handle balls coated with MAP-contaminated dirt. MAP infection is consistent with glioblastoma's two defining histopathologic characteristics: endothelial cell proliferation and pseudopalisading necrosis. MAP is a non-tuberculous or atypical mycobacterium, which can cause hypoxic necrotizing granulomas, granulomas that resemble areas of pseudopalisading necrosis. There are known bacterial causes of endothelial cell proliferation. Almost unique amongst intracellular bacteria, MAP's variant isocitrate dehydrogenase 1 (IDH1) enzyme, a type 2-oxoglutarate ferredoxin oxidoreductase, can use a host cell's cytosolic α-ketoglutarate in its own Krebs or tricarboxylic acid cycle. MAP's ability to use a host cell's α-ketoglutarate may explain the survival advantage of the cytosolic IDH1 enzyme mutation for patients with diffuse gliomas including glioblastoma, astrocytoma, and oligdendroglioma, a mutation that results in a reduced supply of cytosolic α-ketoglutarate. MAP may therefore be one possible infectious cause of glioblastoma and the other histologic categories of diffuse glioma.
Keywords: Diffuse gliomas infectious etiology, Endothelial cell proliferation, *Mycobacterium avium* subspecies *paratuberculosis*, Necrotizing atypical mycobacterial granulomas, Transdifferentiation.

Introduction: Suspected infectious causes of glioma

Infectious agents have been suggested as possible causes of nervous system tumors of several histopathologic types (Altieri *et al*., 2006; Alibek *et al*., 2013). Given their neurotropism, viruses have been the focus of investigation into possible infectious causes of brain cancers (Kofman *et al*., 2011), including the human herpes viruses cytomegalovirus (Pandey, 2011; Dziurzynski *et al*., 2012; Wick and Platten, 2014; Holdhoff *et al*., 2017) and Epstein–Barr virus (Akhtar *et al*., 2018). The parasite *Toxoplasma gondii* is a proposed non-viral infectious cause of brain cancer (Schuman *et al*., 1967; Thirugnanam *et al*., 2013). Two case reports relate the bacteria *Borrelia burgdorferi* to glioblastoma (Colpak *et al*., 2014; MacDonald, 2018).

Zoonoses on ruminant animal farms and the epidemiology of glioblastoma and other diffuse gliomas

There is a long noted increased rate of gliomas, including glioblastoma, in rural residents of Western countries who live in areas where domestic livestock farms are located (Brooks, 1972; Wingren and Axelson, 1992; Howell *et al*., 1995; Hansson and Ferguson, 2011). Farm residents (Choi *et al*., 1970) and farm workers (Musicco *et al*., 1982; Blair *et al*., 1985; Khuder *et al*., 1998), in particular, domestic livestock farmers (Reif *et al*., 1989a,b; Lee *et al*., 2002) including sheep (Reif *et al*., 1989a) and dairy (Milham, 1976; Reif *et al*., 1989a,b; Morrison *et al*., 1992) farmers, have an increased risk for brain cancers, with a predominance of diffuse gliomas including astrocytoma and glioblastoma in one study (Choi *et al*., 1970).

Pesticides have been extensively investigated as the possible reason for the increased rate of gliomas in rural and farm residents and workers but the research has been unable to confirm an association between pesticides and diffuse gliomas (Samanic *et al*., 2008; Yiin *et al*., 2012).

Investigators have occasionally suggested that it is not pesticides but a zoonotic microorganism, an animal virus or bacteria that may be responsible for the

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increased rate of gliomas in rural and farm residents and workers (Carozza *et al*., 2008; Efird *et al*., 2014).

Zoonotic microorganisms are excreted in an infected animal's feces or manure and contaminate the ground the animal is defecating on (Manning and Collins, 2001). Rural residents who live near animal farms, live on animal farms or work on animal farms can become infected with a zoonosis by inhaling, ingesting, or directly contacting or handling pathogen-contaminated manure or manure-contaminated soil, dirt, and dust (The Center for Food Security and Public Health, 2017). Increased rates of glioblastoma in tennis players (Imbriano, 2012) and baseball pitchers (Martinez, 2016; Gartland, 2017), catchers, infield position players, and umpires (Franklin, 2011; Imbriano, 2012), including glioblastoma clusters of American professional baseball players from the Philadelphia Phillies, New York Yankees, and Kansas City Royals (Avril, 2013; Longman, 2017) suggest that the same zoonotic microorganism excreted in an infected domestic ruminant's manure, contaminating the soil of rural environments, may also be present in the baseline soil of baseball fields and in tennis grass and clay courts.

Mycobacterium avium subspecies paratuberculosis: the zoonosis responsible for some cases of diffuse gliomas, including glioblastoma?

Mycobacterium avium subspecies *paratuberculosis* (MAP) is a zoonotic microorganism present in domestic livestock feces or manure that may be responsible for the increased rate of diffuse gliomas, including glioblastoma, in domestic livestock farmers, rural residents living near domestic livestock farms and herds, and baseball and tennis players playing on fields and grass and clay courts far from domestic livestock farms (Pierce, 2017). MAP causes a chronic intestinal disease in domestic ruminants known as Johne's disease (Tiwari *et al*., 2006). MAP is a long suspected cause of Crohn's disease (Uzoigwe *et al*., 2007; Kuenstner *et al*., 2017), but has also been implicated in a wide range of autoimmune diseases (Zhang *et al*., 2017; 2018) as well as the neurologic disorders Parkinson's disease (Dow, 2014; Arru *et al*., 2016) and multiple sclerosis (Sechi and Dow, 2015). A recent study describes MAP antibodies in sera from patients with neuromyelitis optica disorder (Slavin *et al*., 2018). A significant segment of the medical community considers MAP to be a zoonosis (Davis, 2015; Davis *et al*., 2017; Kuenstner *et al*., 2017; Garvey, 2018). Like other zoonoses (Corbel, 2006), MAP may cause a range of diseases in its human host but MAP does not cause in its animal hosts.

MAP in feces or manure and soil and dirt

MAP is heavily excreted in an infected animal's feces or manure (McKenna *et al*., 2006). MAP lasts indefinitely in the environment once excreted, and is diffusely distributed throughout the soil in countries where MAP infection of domestic livestock is long-standing (Rhodes *et al*., 2013).

How to catch MAP and other non-tuberculous or atypical mycobacteria

MAP is a type of non-tuberculous or atypical mycobacterium. Non-tuberculous mycobacteria are environmental mycobacteria, bacteria which are present in soil, dirt, and dust (O'Brien, 1989; Falkinham, 2009; Nishiuchi *et al*., 2017). Other non-tuberculous mycobacteria can be contracted by direct contact with or inhalation of the mycobacterium in dirt or dust. Children who contract non-tuberculous mycobacteria frequently get infected by putting soil or dirt into their mouths (Krantz *et al*., 2016). Baseball pitchers often lick their fingers between pitches after holding balls coated with possibly MAP-contaminated dirt. Baseball catchers crouch in the possibly MAP-contaminated dirt above home base, have dirt thrown into their faces by players running on or sliding into home base, and repeatedly catch and handle balls coated with possibly MAP-contaminated dirt. Baseball infield players are positioned on possibly MAP-contaminated baseline dirt. Tennis players constantly handle tennis balls coated with possibly MAP-contaminated grass, dirt, and clay. Farmers who do not wash their hands after applying pesticides, and probably don't wash their hands after other farm work, have an increased risk of glioma (Ruder *et al*., 2009).

Areas of pseudopalisading necrosis in glioblastoma: are they hypoxic necrotizing mycobacterial granulomas?

MAP may be responsible for the two pathognomonic histologic features of glioblastoma: endothelial cell proliferation and pseudopalisading necrosis. Areas of pseudopalisading necrosis in glioblastomas (Pathpedia, 2018) resemble necrotizing granulomas, which are characterized by a "pseudopalisading" lymphoproliferative reaction (Shah *et al*., 2017). Both tuberculous and non-tuberculous mycobacteria as well as fungi are the major causes of necrotizing granulomas (Shah *et al*., 2017). Necrotizing granulomas come in several shapes. If the location of the granuloma is cutaneous and the lymphoproliferative reaction has a more definite palisading shape, the necrotizing granuloma is described as a palisading granuloma. If the necrosis is in a wavy, curvilinear pattern, it is described as a serpentine granuloma. Non-tuberculous mycobacteria are known causes of palisading (Bartralot *et al*., 2000) and serpentine (University of Medicine and Dentistry of New Jersey, 2018) granulomas. Areas of pseudopalisading necrosis in glioblastoma most closely resemble the palisading and serpentine granulomas caused by non-tuberculous mycobacteria.

Necrosis is not a feature of MAP infection of dairy and beef cattle, but is a feature of MAP infection of goats, sheep, and water buffaloes (Williams *et al*., 1983; Kurade *et al*., 2004; Sivakumar *et al*., 2005).

Granulomas caused by *Mycobacteria* including *Mycobacterium tuberculosis* and non-tuberculous or atypical mycobacteria including *M. avium complex* species (of which MAP is a subspecies) are a result of

hypoxic insult to the mycobacteria-laden macrophages in the center of the granuloma (Via *et al*., 2008; Cardoso *et al*., 2015). Similarly, the areas of pseudopalisading necrosis in glioblastoma are also thought to result from hypoxia (Rong *et al*., 2006).

What is the difference between a mycobacterial granuloma and a possibly MAP-associated glioblastoma granuloma are what the center granuloma cells consist of. In mycobacterial granulomas, the center cells are macrophages. In glioblastoma granulomas, the center cells are glioblastoma tumor cells.

Endothelial cells and "glioblastoma granulomas"

What are glioblastoma tumor cells? Glioblastoma tumor cells show transdiffererentiation with vascular endothelial cells (Ricci-Vitiani *et al*., 2010; Soda *et al*., 2011). Glioblastoma tumor cells can be thought of as malignant vascular endothelial cells. These malignant vascular endothelial glioblastoma cells comprise the areas of pseudopalisading necrosis. Hypoxia within the areas of pseudopalisading necrosis of glioblastomas, which are otherwise characterized as among the most vascular of malignant tumors (Hardee and Zagzag, 2012), is similar to the simultaneous hyperemia and ischemia of the bowel wall in Crohn's disease, another MAP-associated human disease (Hatoum *et al*., 2005).

Granulomas are usually composed of a central area of tissue macrophages called epitheleoid histiocytes. The historical literature on Crohn's disease describes another mechanism of granuloma formation, whereby Crohn's granulomas are composed of non-proliferating lymphatic endothelial cells instead (Hadfield, 1939). Both vascular endothelial cell proliferation (Binion and Rafiee, 2009) and lymphatic endothelial cell proliferation (Hadfield, 1939; Warren and Sommers, 1948) have been described as histopathologic components of idiopathic inflammatory bowel disease. It is possible that the centers of MAP-associated glioblastoma granulomas are composed of MAP-infected vascular endothelial cells.

MAP on the animal and human brain

The evidence that MAP can infect a mammalian brain is almost non-existent. Animals having symptoms, usually gastrointestinal, of MAP infection are culled from a herd, and generally are not necropsied. A single study of goats experimentally infected with MAP demonstrated "cerebrocortical necrosis" in 3 out of 26 infected goats who had "neurological signs" (Kohler *et al*., 2015). The authors did not state whether the cerebrocortical necrosis had a granulomatous histology. Cerebrocortical necrosis or polioencephalomalacia is a disease of ruminant livestock associated with thiamine deficiency or high-sulfate diets (Gould, 1998). The histology of polioencephalomalacia consists of multiple foci of necrosis in the cerebral cortex and endothelial cell proliferation (Adams *et al*., 1956). The necrosis occurs in grey matter rather than white, and is of neurons rather than glial cells.

MAP may have a predilection for the human brain. The normal temperature of a dairy cow, the original and natural animal host of MAP, is 101.5°F. The human brain is the warmest part of the human body, although its "intense heat production" is rapidly cleared by cerebral blood flow, so only a small thermal gradient exists between the brain and the rest of the human body (Wang *et al*., 2014). MAP may prefer the slightly higher temperature of the human brain compared to the rest of the human body.

Is there any evidence of MAP causing vascular endothelial cell hyperplasia?

A study of remote (non-gastrointestinal) MAP lesions in infected goats described MAP organisms being present in the endothelial cells of the intermediate sinuses of lymph nodes, and of causing increased glomerular tufting "due to the proliferation of vascular endothelium" (Sato *et al*., 1968). A tiny literature suggests that endothelial cell proliferation is the precursor of granuloma formation in bovine MAP infection (Liang *et al*., 2016). There are other known bacterial causes of endothelial cell proliferation, including *Mycobacterium lepromatosis* (Han *et al*., 2008) and species of *Bartonella* (Berrich *et al*., 2011).

MAP and the cellular metabolism of diffuse gliomas: the isocitrate dehydrogenase 1 (IDH1) mutation

In the World Health Organization (WHO)'s new (2016) central nervous system tumor classification system (Komori, 2017), diffuse glioma histology, categorized as glioblastoma, astrocytoma, oligodendroglioma, and oligoastrocytoma, has been almost completely superseded by the presence or absence of the isocitrate dehydrogenase 1 (IDH1) mutation (Tateishi *et al*., 2017). According to WHO's new classification, the only characteristic that 'matters' in a diffuse glioma, the most important characteristic in terms of patient survival, is whether or not the diffuse glioma has the IDH1 mutation (Lee, 2018). Patients whose glioblastomas have mutations, primarily the R132H mutation, in the IDH1 enzyme gene have an improved survival rate compared to patients with the wild-type or 'normal' IDH1 gene. How might the wild-type, normal IDH1 enzyme 'help' MAP proliferate or persist in an infected brain, and how might the mutant IDH1 enzyme 'hurt' MAP, suppressing MAP's replication or persistence in an infected brain?

The normal or wild-type IDH1 enzyme catalyzes the conversion of isocitrate to α-ketoglutarate, and vice versa, in the cytoplasm of a eukaryotic cell. α-Ketoglutarate produced by wild-type or normal IDH1 is in the cytosol, and it can either translocate into a mitochondrion and participate in the tricarboxylic acid cycle (TCA) cycle, or it can remain in the cytosol and, via IDH1, undergo reductive carboxylation back into isocitrate, eventually resulting in the acetyl-coenzyme A necessary for lipid synthesis (Maus and Peters, 2017).

Intracellular bacteria usually lack the next enzyme in the TCA cycle, α-ketoglutarate dehydrogenase, needed to convert α-ketoglutarate to succinate (Munoz-Elias and McKinney, 2006). MAP has a unique type of α-ketoglutarate dehydrogenase, called type 2-oxoglutarate (another name for α-ketoglutarate) ferredoxin oxidoreductase, which can convert α-ketoglutarate to succinyl-coenzyme A (Weigoldt, 2012; Weigoldt *et al*., 2013) in MAP's version of the TCA cycle. Wild-type or normal IDH1, therefore, is helpful to MAP, it 'gives' MAP the α-ketoglutarate it needs for its own variant TCA cycle.

The mutant IDH1 enzyme has a reduced ability to convert isocitrate to α-ketoglutarate, and the little α-ketoglutarate that is produced is converted to 2-hydroxyglutarate, resulting in a deficiency of α-ketoglutarate. The lack of α-ketoglutarate in an IDH1-deficient MAP-infected host cell may result in MAP going into a dormant, non-replicating mode. The dormancy of MAP resulting from host α-ketoglutarate deficiency may be responsible for the improved survival rate in diffuse glioma patients with the IDH1 mutation. The fact that the IDH1 mutation occurs in the majority of what the 2016 WHO classification now just calls astrocytomas and oligodendrogliomas and correlates with their improved survival rate suggests that MAP may be involved in the pathogenesis of all diffuse gliomas, not just glioblastoma.

Challenges to the identification of MAP in glioblastoma and other diffuse gliomas

Several obstacles exist in identifying MAP organisms in human tissue. In the United States, laboratories handling animal tissue, that have commercial automated systems for culturing, histopathologic, and immunohistochemical identification of MAP in tissue, are not permitted to process human tissue. Identification of acid fact organisms using traditional acid fast stains require prolonged light microscopic examination at high (oil immersion) magnification (Shah *et al*., 2017). Researchers have noted that MAP organisms are often not found within the histologic lesions of infected animals (Brady *et al*., 2008).

Conclusion: diffuse gliomas, including glioblastoma, as possible MAP-associated brain lesions

There are epidemiologic, cellular metabolic, and histologic suggestions of a possible etiologic relationship between MAP and diffuse gliomas, including glioblastoma. A specific bacterial cause of some cases of diffuse glioma would have implications for their prevention by vaccination (Abdellrazeq *et al*., 2018) and potential response to antimicrobial treatments (Wu *et al*., 2016; RedHill Biopharma, 2017).

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Conflict of interest

The author declares that there is no conflict of interest.

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