CHAPTER 29

MYCOPHENOLIC ACID

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Mycophenolic acid (MPA) is an antiproliferative agent which has recently been used as an immunosuppressive drug.[1] MPA presents in the forms of mycophenolate mophetil (MMF) (CellCept, Roche) and enteric coated mycophenolate sodium (MPS) (Myfortic, Novartis) in the market.

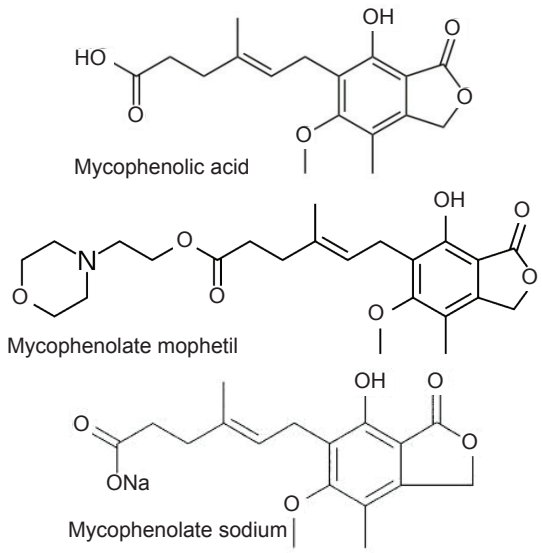

Figure 1. Chemical formulas of mycophenolic acid, mycophenolate mophetil and mycophenolate sodium

CHEMICAL STRUCTURE AND HISTORICAL DEVELOPMENT

MPA was first isolated in 1896 by Gozio as a fermentation product of *Penicillium stoloniferum* cultures. Detailed features were described in 1913 by Alsberg and Black, and MPA was reported as a dibasic acid which was soluble in oil and its formula was defined as $C_{17}H_{20}O_6$.[2] Poor antibacterial, antiviral, antifungal effects of MPA were described subsequently. After the documentation of its antimitotic effects in mammalian cells in 1960, it was accepted as a potential antitumor agent. Inhibition of de novo purine synthesis which was the main mechanism of action was reported by Franklin and Cook.[3] Immunosuppressive features of MPA were described.[4] Effects of MPA on lymphocyte functions were shown.[5] MMF, was developed as a prodrug which was a semi synthetic 2 morpholino ethyl ester form of MPA.[6]

MMF had initially been used in the treatment of rheumatoid arthritis.[7] MPA was started to be used for the treatment of psoriasis in 1975.[8] However, it was discontinued due to its side effects. Clinical trials were held in renal transplant patients in 1988.[9] MMF was approved by FDA in 1995 for prophilaxis and management of rejection treatment after kidney transplantation.[10] MMF was approved for heart transplantation and then for liver transplantation in 2000 to prevent allograft rejection.[10] In the following years, MPS salt was developed subsequently to reduce gastrointestinal side effects.[11] (Figure 1). MMF and MPS are both hydrolyzed into MPA in intestine, blood, liver and tissue.[12]

MECHANISMS OF ACTION

MPA is a powerful, selective, noncompetitive and reversible inhibitor of inosine-5'-monophosphate dehydrogenase (IMPDH) which is a rate-limiting enzyme in the synthesis of de novo guanosine monophosphate.[5] MPA is more sensitive for IMPDH type 2 which is specific to lymphocytes whereas type I is expressed in most cell types.[13] MPA reduces guanosin and deoxyguanosine nucleotides in T and B lymphocytes and therefore inhibits the production of immunoglobulins. Although MPA reduces guanosine triphosphate and deoxyguanosine triphosphate in lymphocytes, the same effect is not seen in neutrophils. Hypoxanthine guanine phosphoribosyltransferase (HGPRT) salvage pathway may also contribute to the purine synthesis. However, this pathway exists in most of the cells except lymphocytes. This contributes to the more selective inhibition of lymphocytes by MPA whereas other cells are relatively spared.[10] Besides, MPA inhibits maturation of dendritic cells and reduces antigen presentation to T lymphocytes. MPA decreases the activity of monocytes in graft rejection and inflammation region.[1,14,15]

MMF has antiinflammatory activity. MMF inhibits the glycosylation of lymphocytes and monocytes glycoproteins which participate in adhesion to the endothelial cells. Thus, adhesion of lymphocytes and monocytes

calcineurin inhibitors stimulate transforming growth factor-beta which is fibrogenic whereas MMF does not. MMF inhibits arterial smooth muscle cell proliferation and does not increase blood pressure, cholesterol, and triglycerides levels. Besides, it reduces HDL oxidation.[62]

POTENTIAL USES IN THE FUTURE

Recent studies focused on whether MMF has potential role in the treatment of atherosclerosis due to its antiproliferative and proapopitotic effects of MMF on T cells, antiatherogenic effects on endothelial cells, monocytes and macrophages, smooth muscle cells and dendritic cells and antioxidative effects.[63]

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