

丙酮醛抗肿瘤机制的研究进展

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摘要 丙酮醛作为正常的生理代谢产物, 可来源于多条代谢通路, 最主要的来源是糖酵解途径, 丙酮醛分解主要是在乙二醛酶系统的作用下最终转化为D-乳酸。丙酮醛具有高度的活性和细胞毒性, 它在多种类型的肿瘤组织中含量较低。丙酮醛能够抑制恶性肿瘤细胞的增殖、诱导其凋亡、抑制肿瘤的转移, 并能通过增强机体的免疫力以及提高对现有抗肿瘤药物的敏感性等作用更进一步地发挥抗肿瘤效应。深入研究其抗肿瘤机制能够为临床试验提供依据、使其成为有潜力的新型抗肿瘤药, 该文就丙酮醛可能的作用机制予以综述。

关键词 丙酮醛; 抗肿瘤; 机制

Advance on the Anti-tumor Mechanism of Methylglyoxal

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Abstract As a normal physiological metabolites, methylglyoxal (MG) is formed from various metabolic routes, among them glycolytic pathway provides the most important source. MG is mainly catalyzed by glyoxalasesystem, it converts to D-lactate finally. MG is highly reactive and it processes cell toxicity. MG is lower in many types of cancers. The anticancer effect of MG is due to its anti-proliferative properties, the abilities of inducing apoptosis and inhibiting tumor metastasis, it can also enhance immune system and increase sensitivity to antitumor agents. Further investigation of the mechanisms will provide evidences for next stage clinical research and make this compound to be a potential therapeutic agent, the aim of this review is to summarize the mechanisms of MG's antitumor effect.

Keywords methylglyoxal; anti-tumor; mechanism

丙酮醛是人体内正常的代谢产物, 可由碳水化合物、脂质及蛋白质代谢产生, 正常生理情况下它在人体内的合成量极低, 而在高血糖状态下如糖尿病患者体内会显著增高, 丙酮醛是一种高活性化合物并具有细胞毒性^[1-2]。早在1958年, 人们发现丙酮醛不仅具有抗疟疾、抗病毒的作用而且有抗肿瘤的效应^[3], 随后人们从体外、体内实验以及临床患论证了丙酮醛的抗肿瘤作用^[4], 现将丙酮醛的代谢

过程及其抗肿瘤作用机制的研究进展综述如下。

1 丙酮醛的代谢

1.1 丙酮醛的合成

丙酮醛是一种小分子的高活性二羰基复合物, 丙酮醛的合成广泛存在于人体内各种组织和细胞中^[5]。如图1所示, 丙酮醛可来源于多条代谢通路, 最主要的是来自于糖酵解途径, 由磷酸丙酮、三磷

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酸甘油醛和磷酸二羟丙酮裂解产生^[6]。这一产生途径可以是非酶促反应,也可以是酶促反应^[7]。酶促反应是由磷酸丙糖异构酶^[8]和丙酮醛合酶催化的^[9]。另外,丙酮醛同样也是蛋白质和脂肪酸代谢过程中的副产物,细胞色素P450 2E1分解酮体时会催化生成丙酮醇和丙酮醛^[10];在苏氨酸代谢过程中氨基丙酮的氧化^[11]以及糖基化蛋白质的降解也会产生丙酮醛^[12]。丙酮醛的合成速率约为125 $\mu\text{mol/kg}$ 细胞量/d^[13],按照成年人约25 kg细胞量来计算^[14],每天人体内丙酮醛的合成量约为3 mmol。细胞和组织内丙酮醛的浓度通常是2~4 $\mu\text{mol/L}$,正常人血浆中约为0.1 $\mu\text{mol/L}$ ^[15]。

1.2 丙酮醛的分解

丙酮醛的分解代谢有乙二醛酶、醛糖还原酶、醛脱氢酶以及羧基还原酶途径等^[5],最主要的分解途径是乙二醛酶系统。乙二醛酶系统包括乙二醛酶I和乙二醛酶II,还原型谷胱甘肽为辅助因子。丙酮醛能够与还原型谷胱甘肽经非酶促反应自发形成缩醛,它能与乙二醛酶I(glyoxalase I, GLO1)的两个活性位点结合,在乙二醛酶I催化作用下转化成S-D-乳酸谷胱甘肽^[16]。继而在乙二醛酶II(glyoxalase II, GLO2)的作用下,S-D-乳酸谷胱甘肽被水解成D-乳酸,同时重新生成还原型谷胱甘肽并进入乙二醛酶I催化的第一步反应中被循环利用^[17](图1)。D-乳酸能够在线粒体中被2-羟基酸脱氢酶代谢合成丙酮酸^[1]。

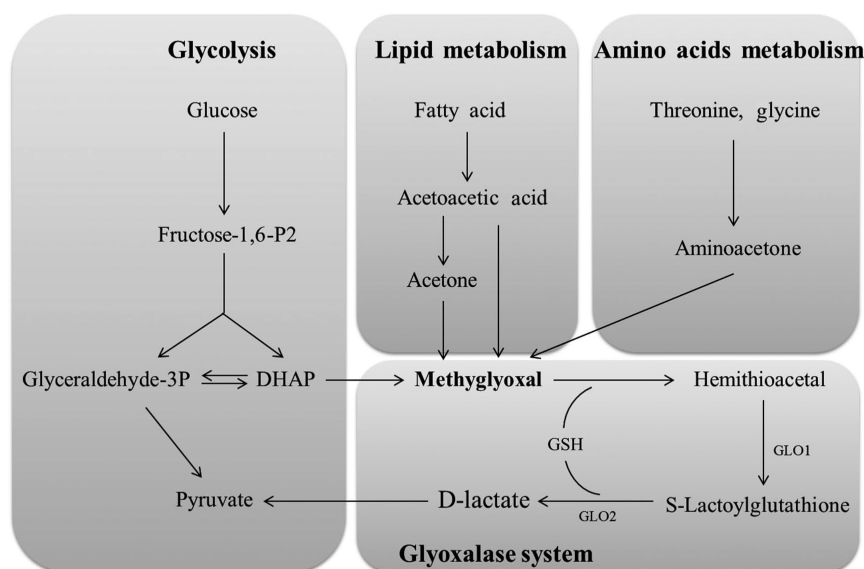
乙二醛酶I是丙酮醛分解过程中的关键酶,它的活性程度会直接影响丙酮醛浓度的高低。

2 丙酮醛的抗肿瘤机制

丙酮醛具有极高的活性,能够与蛋白质、核酸等生物大分子反应并对其修饰,从而导致细胞功能改变。研究表明,丙酮醛具有多种细胞毒性作用,如抑制细胞生长、诱导细胞凋亡、抑制酶的活性以及激活信号通路等^[18]。丙酮醛在多种类型肿瘤组织中的含量比正常组织中低^[19-20],在干扰乙二醛酶或者加入乙二醛酶抑制后可出现明显的肿瘤抑制作用,而这一抑制作用是通过升高丙酮醛浓度实现的^[21]。丙酮醛可通过抑制增殖、诱导凋亡、抑制肿瘤转移以及增强机体的免疫力和提高对现有抗肿瘤药物的敏感性等方面发挥抗肿瘤效应。

2.1 抑制增殖

早在19世纪60年代,丙酮醛就被认为是天然的生长调节因子,是一种抑素,能够阻止细胞分裂^[22]。丙酮醛能够抑制人白血病HL-60细胞的生长^[23],并能够抑制接种了艾氏腹水癌(Ehrlich ascites carcinoma, EAC)细胞、白血病L4946细胞、腺癌细胞及肉瘤S180细胞等的荷瘤小鼠体内肿瘤的生长^[24],说明丙酮醛能够抑制肿瘤细胞的增殖。研究表明,其抑制增殖的机制在于它能够抑制蛋白质的合成^[25],丙酮



DHAP: 磷酸二羟丙酮; GSH: 谷胱甘肽。

DHAP: dihydroxy acetone phosphate; GSH: glutathione.

图1 丙酮醛的主要代谢通路

Fig.1 Main metabolic pathways involved in methylglyoxal production and elimination

醛能够修饰RNA的鸟苷酸残基导致蛋白质聚合体稳定性下降,从而阻滞蛋白质合成的起始过程^[26]。丙酮醛还能够与DNA的咪基残基端发生反应对其进行修饰,从而使DNA双链断裂、形成DNA-蛋白质交联物等抑制DNA的合成,同时丙酮醛也会轻微的影响RNA的合成^[26]。随后人们发现,丙酮醛可以通过影响代谢进而抑制肿瘤细胞的增殖,一方面,丙酮醛能够干预肿瘤细胞的糖酵解过程,研究表明,用2 mmol/L和5 mmol/L的丙酮醛作用于ECA细胞后,葡萄糖的利用分别被抑制50%和80%,乳酸生成量分别被抑制55%和90%,并发现丙酮醛能够极大地抑制恶性肿瘤细胞中3-磷酸甘油醛脱氢酶的活性^[27],由于肿瘤细胞赖以生存及快速增殖的原料来自于其活跃的低氧糖酵解过程^[28],因而丙酮醛能够有效并特异地抑制其增殖;另一方面,丙酮醛直接抑制线粒体氧化呼吸过程,主要是通过抑制线粒体复合物I参与的电子链传递导致肿瘤细胞的氧耗和ATP的生成减少从而极大地削减了能量供应^[29]。此外,丙酮醛还能阻止细胞由DNA合成前期(G₁期)向DNA合成期(S期)转变,它首先下调前列腺癌PC3细胞周期蛋白cyclinD1的表达,继而下调细胞周期蛋白依赖性激酶2(cyclin-dependent kinase 2, cdk2)和cdk4,使视网膜母细胞瘤蛋白(retinoblastoma protein, pRB)去磷酸化最终导致G₁期阻滞、生长停止^[30]。因此,丙酮醛能够通过抑制蛋白质、DNA合成,抑制肿瘤细胞的

糖酵解和氧化磷酸化过程以及调节细胞周期等抑制肿瘤细胞的增殖。

2.2 诱导凋亡

近年来人们发现,丙酮醛发挥抗肿瘤作用最主要的途径是通过诱导细胞凋亡,研究表明,将丙酮醛作用于包括前列腺癌细胞、肝癌细胞、肉瘤细胞等在内的多种恶性肿瘤细胞后,细胞的形态发生极大改变并裂解、细胞内DNA碎片增多并形成凋亡小体等^[31-33]。丙酮醛诱发凋亡的机制有以下几种(图2)。(1)丙酮醛能使细胞内活性氧(reactive oxygen species, ROS)水平升高,丙酮醛在糖基化反应过程中产生的超氧化物阴离子和过氧化氢以及它对ROS清除酶类的抑制分别从增加来源与减少去路两方面提高了细胞内ROS的生成量^[34]。升高的ROS可作为上游信号分子激活分裂原激活的蛋白激酶p38(p38 mitogen activated protein kinases, p38MAPK)、p42/44MAPK信号通路介导细胞凋亡^[34-35];同时ROS的产生还能触发线粒体释放细胞色素c,进而激活细胞凋亡蛋白酶caspase-3、caspase-9,并下调DNA修复酶聚腺苷二磷酸-核糖聚合酶(poly ADP-ribose polymerase, PARP)进一步损伤细胞^[30,32]。(2)丙酮醛作为强大的糖化剂能够与蛋白质等其他胞内重要成分发生糖化反应产生晚期糖化终末产物(advanced glycation end products, AGEs),其中,精氨嘧啶(argpyrimidine, AP)是丙酮醛修饰蛋白质的精氨酸残基后主要的产物之

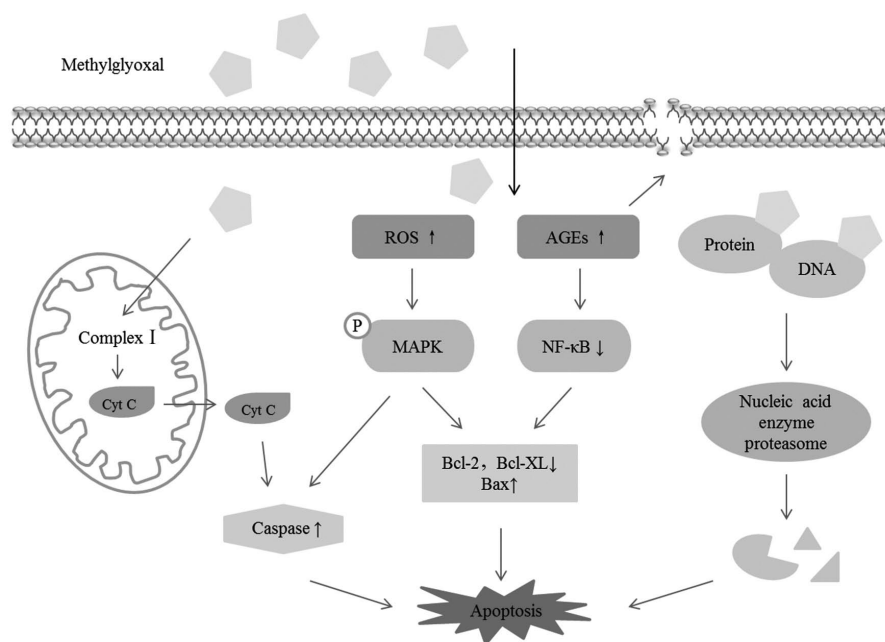


图2 丙酮醛诱导凋亡的机制

Fig.2 The mechanism of apoptosis induced by methylglyoxal

一,它能够在激活核转录因子NF- κ B(nuclear factor-Kappa B)信号通路,触发线粒体凋亡机制的同时上调凋亡蛋白Bax(Bcl-2-associated X protein)、下调抗凋亡蛋白Bcl-2(B-cell lymphoma-2)和Bcl-XL的表达,最终导致细胞凋亡增加;AP还能通过直接破坏细胞骨架蛋白肌动蛋白actin和微管蛋白 α -tubulin来促进凋亡^[31]。(3)在对肉瘤的研究中发现,丙酮醛在降低线粒体复合物I活性的过程中,除了能极大地降低ATP的产生外,还能够降低线粒体跨膜电位,进而改变线粒体膜通透性,释放线粒体促凋亡因子细胞色素c,最终破坏线粒体膜的完整性并导致细胞死亡^[33]。因此,丙酮醛能够通过直接或间接的方式激活凋亡信号通路以及线粒体凋亡途径促进凋亡。另外,丙酮醛对DNA残基进行糖化修饰形成的MG-DNA加合物能够激活核酸内切酶类^[26],对蛋白质进行修饰后,蛋白质的生物活性与稳定性会受到一定影响,甚至会被蛋白酶体识别而降解^[36],这些也是丙酮醛促进凋亡的原因之一。

2.3 抑制侵袭、黏附能力

肿瘤细胞的黏附、迁移以及侵袭能力是肿瘤进行转移的必备的关键因素。丙酮醛能够抑制肝癌Huh-7和HepG2细胞的黏附与侵袭能力,这一抑制作用是由抑癌基因p53介导的,当p53被抑制或干扰后则不存在这一抑制作用。丙酮醛能促进p53转运至核内增强它的转录活性,并将Y220C突变型p53恢复至野生型p53所具有的构象和活性^[37],随着野生型p53功能的恢复肿瘤细胞的移动和侵袭受到抑制,而恢复p53功能已被推荐为抗肿瘤治疗的一种^[38],因此丙酮醛能够通过p53途径抑制肝癌的转移。

2.4 免疫调节

免疫调节已被认为是预防和治疗肿瘤的另一种选择,免疫系统的防御机制主要是通过主动或被动免疫激活机体免疫应答来清除肿瘤细胞,预防肿瘤转移和复发。研究表明,丙酮醛能够增加肉瘤180细胞小鼠模型体内巨噬细胞的数量和吞噬能力以及杀伤性T细胞的产生和杀伤作用,增强小鼠的细胞免疫以抵抗肿瘤^[39],同时小鼠体内一些免疫调节因子和表面受体:干扰素- γ (interferon- γ , IFN- γ)、肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α)、白细胞介素-1 β (interleukin-1 β , IL-1 β)、IL-6、Toll样受体-4(toll-like receptor-4, TLR-4)以及TLR-9也的表达出现明显的升高^[40]。丙酮醛主要通过调节巨噬细胞集落

刺激因子促进巨噬细胞的产生, p38MAPK、NF- κ B信号通路也参与其中^[41]。因此,丙酮醛在增强巨噬细胞和淋巴细胞的活性以及通过免疫调节抵抗肿瘤过程中发挥着重要的作用。

2.5 提高化疗药物敏感性

乙二醛酶I的高表达会引起多柔比星、依托泊苷、丝裂霉素C及其他化疗药物的多重耐药。研究发现,许多对现有的临床化疗药物多重耐药的人类肿瘤细胞系中乙二醛酶I的mRNA水平普遍较高,上调非多重耐药的肿瘤细胞内乙二醛酶I的表达量后该细胞也会出现多重耐药现象^[42]。乙二醛酶I高表达引起化疗药物的多重耐药的具体机制现在尚不清楚,但可以肯定的是与丙酮醛密切相关,将乙二醛酶I抑制剂对溴苯甲基谷胱甘肽环戊二酯作用于细胞后,细胞内丙酮醛含量明显升高,且细胞重新获得对抗肿瘤药物的敏感性^[43]。另外,有文献报道,丙酮醛能够通过激活蛋白激酶C(protein kinase C, PKC)的 δ 亚基来增强顺铂对骨髓瘤细胞的杀伤作用,联合丙酮醛可将顺铂的抗肿瘤效应放大约4倍^[44]。

3 结语与展望

丙酮醛的抗肿瘤效应已在体外实验、体内实验以及临床肿瘤治疗中得以证实,但丙酮醛的作用机制十分复杂。有研究报道认为,丙酮醛对热休克蛋白27(heat shock protein 27, Hsp27)修饰后可促使大鼠胃癌RGK-1细胞及人结直肠癌HT-29细胞逃避凋亡^[45],但犹如氧化应激具有致癌效应的同时也能够发挥抗肿瘤作用一样,丙酮醛也具有双面性,是细胞毒性化合物还是致癌因子主要依赖于整体的胞内环境^[46]。丙酮醛用于抗肿瘤治疗最大的优点是,丙酮醛能够特异地抑制恶性肿瘤细胞的糖酵解和氧化磷酸化,而对正常细胞的线粒体呼吸并无抑制作用^[47],在同样的条件下,丙酮醛能针对性的抵抗恶性肿瘤细胞,但对分化的细胞、中性粒细胞等无毒性作用^[4],且在丙酮醛对荷瘤小鼠的治疗期间并未发现毒副作用^[48]。

综上所述,丙酮醛能够抑制恶性肿瘤细胞增殖、诱导其凋亡,抑制肿瘤细胞转移,并能通过增强机体的免疫力以及提高对现有抗肿瘤药物的敏感性等作用发挥抗肿瘤效应。同时,它还能够特异性地作用于恶性肿瘤细胞,就目前细胞水平和动物水平的研究结果而言,丙酮醛具有一定的安全性。因而,

丙酮醛的研究具有广泛的应用价值, 丙酮醛的抗肿瘤效应可以转化为正在遭受肿瘤磨难的患者们的福音, 期待更多的研究学者和临床医生进行进一步的临床试验。只有经过对癌症患者的治疗后, 才能对丙酮醛的抗肿瘤疗效做出正确的评价, 才能对其有效的使用做出完善的规划。

参考文献 (References)

- Thornalley PJ. The glyoxalase system in health and disease. *Mol Aspects Med* 1993; 14(4): 287-371.
- Lu J, Randell E, Han Y, Adeli K, Krahn J, Meng QH. Increased plasma methylglyoxal level, inflammation, and vascular endothelial dysfunction in diabetic nephropathy. *Clin Biochem* 2011; 44(4): 307-11.
- French FA, Freedlander BL. Carcinostatic action of polycarbonyl compounds and their derivatives. I. 3-Ethoxy-2-ketobutyraldehyde and related compounds. *Cancer Res* 1958; 18(2): 172-5.
- Talukdar D, Ray S, Ray M, Das S. A brief critical overview of the biological effects of methylglyoxal and further evaluation of a methylglyoxal-based anticancer formulation in treating cancer patients. *Drug Metabol Drug Interact* 2008; 23(1/2): 175-210.
- Allaman I, Belanger M, Magistretti PJ. Methylglyoxal, the dark side of glycolysis. *Front Neurosci* 2015; 9: 23.
- Richard JP. Mechanism for the formation of methylglyoxal from triosephosphates. *Biochem Soc Trans* 1993; 21(2): 549-53.
- Thornalley PJ. Pharmacology of methylglyoxal: Formation, modification of proteins and nucleic acids, and enzymatic detoxification—a role in pathogenesis and antiproliferative chemotherapy. *Gen Pharmacol* 1996; 27(4): 565-73.
- Pompliano DL, Peyman A, Knowles JR. Stabilization of a reaction intermediate as a catalytic device: Definition of the functional role of the flexible loop in triosephosphate isomerase. *Biochemistry* 1990; 29(13): 3186-94.
- Ray S, Ray M. Isolation of methylglyoxal synthase from goat liver. *J Biol Chem* 1981; 256(12): 6230-3.
- Reichard GA Jr, Skutches CL, Hoeldtke RD, Owen OE. Acetone metabolism in humans during diabetic ketoacidosis. *Diabetes* 1986; 35(6): 668-74.
- Lyles GA, Chalmers J. The metabolism of aminoacetone to methylglyoxal by semicarbazide-sensitive amine oxidase in human umbilical artery. *Biochem Pharmacol* 1992; 43(7): 1409-14.
- Thornalley PJ, Langborg A, Minhas HS. Formation of glyoxal, methylglyoxal and 3-deoxyglucosone in the glycation of proteins by glucose. *Biochem J* 1999; 344(Pt 1): 109-16.
- Thornalley PJ. Modification of the glyoxalase system in human red blood cells by glucose *in vitro*. *Biochem J* 1988; 254(3): 751-5.
- Ellis KJ. Human body composition: *In vivo* methods. *Physiol Rev* 2000; 80(2): 649-80.
- Rabbani N, Thornalley PJ. Methylglyoxal, glyoxalase 1 and the dicarbonyl proteome. *Amino Acids* 2012; 42(4): 1133-42.
- Mannervik B, Ridderstrom M. Catalytic and molecular properties of glyoxalase I. *Biochem Soc Trans* 1993; 21(2): 515-7.
- Vander Jagt DL. Glyoxalase II: Molecular characteristics, kinetics and mechanism. *Biochem Soc Trans* 1993; 21(2): 522-7.
- Kalapos MP. Methylglyoxal in living organisms: Chemistry, biochemistry, toxicology and biological implications. *Toxicol Lett* 1999; 110(3): 145-75.
- Santarius T, Bignell GR, Greenman CD, Widaa S, Chen L, Mahoney CL, *et al*. GLO1-A novel amplified gene in human cancer. *Genes Chromosomes Cancer* 2010; 49(8): 711-25.
- Fonseca-Sanchez MA, Rodriguez Cuevas S, Mendoza-Hernandez G, Bautista-Pina V, Arechaga Ocampo E, Hidalgo Miranda A, *et al*. Breast cancer proteomics reveals a positive correlation between glyoxalase 1 expression and high tumor grade. *Int J Oncol* 2012; 41(2): 670-80.
- Geng X, Ma J, Zhang F, Xu C. Glyoxalase I in tumor cell proliferation and survival and as a potential target for anticancer therapy. *Oncol Res Treat* 2014; 37(10): 570-4.
- Egyud LG, Szent-Gyorgyi A. On the regulation of cell division. *Proc Natl Acad Sci USA* 1966; 56(1): 203-7.
- Ayoub FM, Allen RE, Thornalley PJ. Inhibition of proliferation of human leukaemia 60 cells by methylglyoxal *in vitro*. *Leuk Res* 1993; 17(5): 397-401.
- Apple MA, Greenberg DM. Arrest of cancer in mice by therapy with normal metabolites. II. Indefinite survivors among mice treated with mixtures of 2-oxopropanal (NSC-79019) and 2,3-dihydroxypropanal (NSC67934). *Cancer Chemother Rep* 1968; 52(7): 687-96.
- Kozarich JW, Deegan JL. 7-Methylguanosine-dependent inhibition of globin mRNA translation by methylglyoxal. *J Biol Chem* 1979; 254(19): 9345-8.
- Kang Y, Edwards LG, Thornalley PJ. Effect of methylglyoxal on human leukaemia 60 cell growth: Modification of DNA G1 growth arrest and induction of apoptosis. *Leuk Res* 1996; 20(5): 397-405.
- Halder J, Ray M, Ray S. Inhibition of glycolysis and mitochondrial respiration of Ehrlich ascites carcinoma cells by methylglyoxal. *Int J Cancer* 1993; 54(3): 443-9.
- Vander Heiden MG, Cantley LC, Thompson CB. Understanding the Warburg effect: the metabolic requirements of cell proliferation. *Science* 2009; 324(5930): 1029-33.
- Ray S, Dutta S, Halder J, Ray M. Inhibition of electron flow through complex I of the mitochondrial respiratory chain of Ehrlich ascites carcinoma cells by methylglyoxal. *Biochem J* 1994; 303(1): 69-72.
- Milanesa DM, Choudhury MS, Mallouh C, Tazaki H, Konno S. Methylglyoxal-induced apoptosis in human prostate carcinoma: Potential modality for prostate cancer treatment. *Eur Urol* 2000; 37(6): 728-34.
- Antognelli C, Mezzasoma L, Fettucciari K, Talesa VN. A novel mechanism of methylglyoxal cytotoxicity in prostate cancer cells. *Int J Biochem Cell Biol* 2013; 45(4): 836-44.
- Chan WH, Wu HJ, Hsuw YD. Curcumin inhibits ROS formation and apoptosis in methylglyoxal-treated human hepatoma G2 cells. *Ann N Y Acad Sci* 2005; 1042: 372-8.
- Ghosh A, Bera S, Ray S, Banerjee T, Ray M. Methylglyoxal induces mitochondria-dependent apoptosis in sarcoma. *Biochemistry (Mosc)* 2011; 76(10): 1164-71.

- 34 Figarola JL, Singhal J, Rahbar S, Awasthi S, Singhal SS. LR-90 prevents methylglyoxal-induced oxidative stress and apoptosis in human endothelial cells. *Apoptosis* 2014; 19(5): 776-88.
- 35 Lü Q, Gu C, Chen C. Venlafaxine protects methylglyoxal-induced apoptosis in the cultured human brain microvascular endothelial cells. *Neurosci Lett* 2014; 569: 99-103.
- 36 Bento CF, Fernandes R, Ramalho J, Marques C, Shang F, Taylor A, *et al.* The chaperone-dependent ubiquitin ligase CHIP targets HIF-1 α for degradation in the presence of methylglyoxal. *PLoS One* 2010; 5(11): e15062.
- 37 Loarca L, Sassi-Gaha S, Artlett CM. Two α -dicarbonyls downregulate migration, invasion, and adhesion of liver cancer cells in a p53-dependent manner. *Dig Liver Dis* 2013; 45(11): 938-46.
- 38 Feldser DM, Kostova KK, Winslow MM, Taylor SE, Cashman C, Whittaker CA, *et al.* Stage-specific sensitivity to p53 restoration during lung cancer progression. *Nature* 2010; 468(7323): 572-5.
- 39 Bhattacharyya N, Pal A, Patra S, Haldar AK, Roy S, Ray M. Activation of macrophages and lymphocytes by methylglyoxal against tumor cells in the host. *Int Immunopharmacol* 2008; 8(11): 1503-12.
- 40 Chakrabarti A, Talukdar D, Pal A, Ray M. Immunomodulation of macrophages by methylglyoxal conjugated with chitosan nanoparticles against Sarcoma-180 tumor in mice. *Cell Immunol* 2014; 287(1): 27-35.
- 41 Pal A, Bhattacharya I, Bhattacharya K, Mandal C, Ray M. Methylglyoxal induced activation of murine peritoneal macrophages and surface markers of T lymphocytes in sarcoma-180 bearing mice: Involvement of MAP kinase, NF-kappa beta signal transduction pathway. *Mol Immunol* 2009; 46(10): 2039-44.
- 42 Thornalley PJ, Rabbani N. Glyoxalase in tumorigenesis and multidrug resistance. *Semin Cell Dev Biol* 2011; 22(3): 318-25.
- 43 Sakamoto H, Mashima T, Kizaki A, Dan S, Hashimoto Y, Naito M, *et al.* Glyoxalase I is involved in resistance of human leukemia cells to antitumor agent-induced apoptosis. *Blood* 2000; 95(10): 3214-8.
- 44 Godbout JP, Pesavento J, Hartman ME, Manson SR, Freund GG. Methylglyoxal enhances cisplatin-induced cytotoxicity by activating protein kinase C δ . *J Biol Chem* 2002; 277(4): 2554-61.
- 45 Oya-Ito T, Naito Y, Takagi T, Handa O, Matsui H, Yamada M, *et al.* Heat-shock protein 27 (Hsp27) as a target of methylglyoxal in gastrointestinal cancer. *Biochim Biophys Acta* 2011; 1812(7): 769-81.
- 46 Chiavarina B, Nokin MJ, Durieux F, Bianchi E, Turtoi A, Peulen O, *et al.* Triple negative tumors accumulate significantly less methylglyoxal specific adducts than other human breast cancer subtypes. *Oncotarget* 2014; 5(14): 5472-82.
- 47 Biswas S, Ray M, Misra S, Dutta DP, Ray S. Selective inhibition of mitochondrial respiration and glycolysis in human leukaemic leucocytes by methylglyoxal. *Biochem J* 1997; 323(Pt 2): 343-8.
- 48 Ghosh M, Talukdar D, Ghosh S, Bhattacharyya N, Ray M, Ray S. *In vivo* assessment of toxicity and pharmacokinetics of methylglyoxal. Augmentation of the curative effect of methylglyoxal on cancer-bearing mice by ascorbic acid and creatine. *Toxicol Appl Pharmacol* 2006; 212(1): 45-58.