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硒蛋白对人体健康重要作用的研究进展

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摘要 硒(selenium, Se)是动物和人类健康所必需的微量元素, 硒的缺乏会导致多种疾病的发生. 硒在体内主要以硒蛋白的形式发挥生物学作用, 目前硒蛋白与人体健康关系的研究日益受到重视. 迄今人类已发现25种硒蛋白, 本文重点对谷胱甘肽过氧化物酶(glutathione peroxidase, GPX)、硫氧还蛋白还原酶(thioredoxin reductase, TrxR)、碘甲状腺氨酸脱碘酶(iodothyronine deiodinase, ID)家族的结构和生物学功能及其与疾病关系等方面进行了综述, 表明GPX、TrxR、ID等硒蛋白具有抗氧化、抗炎症、抗细胞凋亡, 参与甲状腺激素代谢, 调节机体代谢等生物学功能, 可通过遗传与表观遗传等多种形式在肿瘤、心血管疾病、骨关节炎、地方病以及新型冠状病毒肺炎等疾病的发病机制及防治方面起重要作用. 本文为进一步揭示硒蛋白在人体健康中的作用及筛选疾病防治靶标提供新的线索和依据.

关键词 硒蛋白, 硒, 人体健康, 疾病, 生物学功能

硒(selenium, Se)是动物和人类健康所必需的微量营养素, 在体内具有抗氧化、免疫调节、拮抗毒素等作用, 硒的缺乏会导致多种疾病的发生. 然而硒在体内主要以硒蛋白的形式发挥生物学作用, 近年来硒蛋白与人体健康的关系日益受到重视. 研究表明, 硒蛋白在肿瘤、心血管疾病、骨关节炎、地方病以及新型冠状病毒肺炎等疾病的发病机制及防治方面起着重要作用. 因此, 本文将从硒蛋白的结构、生物学功能、分类以及与疾病关系等方面进行综述, 以期为进一步研究硒蛋白在人体健康中的作用提供理论基础.

1 硒蛋白的结构与种类

硒在人体内主要以硒代半胱氨酸(selenocysteine, Sec)和硒代蛋氨酸(selenomethionine, Se-Met)两种形式与蛋白质结合. Sec是由密码子UGA介导的翻译行为, Se-Met则通过随机替代蛋氨酸参与到蛋白质分子中, 其中最有可能是由于甲硫氨酰-tRNA合成酶的耐受性而被掺入蛋白质中[1,2]. 一般把硒以Sec形式参与形成的蛋白质称为硒蛋白(selenoprotein), 而把其他结合硒的蛋白质称为含硒蛋白(Se-containing protein). 原核细胞中硒蛋白mRNA上UGA下游的茎-环结构以及4种基因产物SELA、SELB、SELC、SELD参与了Sec合成硒蛋白的过程. 真核细胞中硒蛋白mRNA 3′端非编码区(3′-UTR)存在硒代半胱氨酸插入序列(SECIS), 作为UGA再编码事件的顺式调控元件. Sec是最新发现的第21种组成机体蛋白质的氨基酸, 是机体有机硒最主要的存在形式, 对人体健康有着至关重要的作用[3].

迄今人类已发现25种硒蛋白, 包括5种谷胱甘肽过氧化物酶(glutathione peroxidase, GPX)、3种硫氧还蛋白还原酶(thioredoxin reductase, TrxR)、3种碘甲状腺

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氨酸脱碘酶(iodothyronine deiodinase, ID)、硒磷酸合成酶(selenium phosphorylates synthetase, SPS)、硒蛋白H(selenoprotein H, SelH)、硒蛋白T(selenoprotein T, SelT)、硒蛋白W(selenoprotein W, SelW)、硒蛋白O(selenoprotein O, SelO)、硒蛋白P(selenoprotein P, SelP)、硒蛋白N(selenoprotein N, SelN)、硒蛋白M(selenoprotein M, SelM)、硒蛋白S(selenoprotein S, SelS)、硒蛋白I(selenoprotein I, SelI)、硒蛋白K(selenoprotein K, SelK)、硒蛋白15(15 kD selenoprotein, Sel15)、硒蛋白R(selenoprotein R, SelR)、硒蛋白V(selenoprotein V, SelV).

2 生物学功能

目前硒蛋白生物学功能研究已成为热点，研究表明，硒蛋白可参与调节细胞氧化应激、内质网应激、抗氧化防御、免疫应答和炎症反应等生物学过程[4]，包括如抗氧化、抗炎症、抗细胞凋亡、抑制转录因子活性、促进精子成熟/保护、参与细胞氧化还原能力和甲状腺激素代谢等[5,6]. 缺硒可造成硒蛋白含量和活性降低，细胞正常生理功能紊乱. 因此，充分了解硒蛋白的功能有助于解释硒缺乏对人体健康的不利影响. 尽管某些硒蛋白功能尚不清楚，但大多硒蛋白在人体健康中的重要作用已日益显露. 目前GPX、ID及TrxR家族的生物学功能研究较为明确，它们主要参与氧化还原信号调节、氧化还原稳态和甲状腺激素代谢等过程[7]，GPX、ID及TrxR家族的生物学功能如下所述.

2.1 谷胱甘肽过氧化物酶家族

GPXs属于抗氧化酶家族，是哺乳动物体内一类重要的含硒酶. Sec是GPXs的活性中心，其活性与机体硒水平密切相关[8]，许多研究采用GPXs活性和表达作为硒状态的生物标志物. 迄今为止，哺乳动物体内共有8种谷胱甘肽过氧化物酶(GPX1、GPX2、GPX3、GPX4、GPX5、GPX6、GPX7和GPX8)，其中GPX1、GPX2、GPX3、GPX4和某些物种的GPX6均含有硒元素，具有抗氧化功能[9].

GPXs生物学功能主要依赖谷胱甘肽(glutathione, GSH)而实现，即通过GSH作为硫醇供体还原机体代谢过程中产生的过氧化氢(hydrogen peroxide, H_2O_2)及脂质过氧化物等有害物质，调节细胞微环境进而实现机体解毒作用，维持细胞的结构完整性及正常功能[10]. 在减轻炎症过程中，GPXs通过调控活性氧(reactive oxygen species, ROS)发挥抗炎作用[11].

2.2 硫氧还蛋白还原酶家族

TrxRs是含硒吡啶核苷酸-二硫化物氧化还原酶家族一员，是一种还原型辅酶(nicotinamide adenine dinucleotide phosphate, NADPH)依赖的包含黄素腺嘌呤二核苷酸(flavin adenine dinucletide, FAD)结构域的二聚体硒酶[12]. 哺乳动物中TrxRs主要有3种类型：TrxR1、TrxR2、TrxR3，分别被*TXNRD1*、*TXNRD2*、*TXNRD3*基因编码. 其中TXNRD1主要存在于细胞浆，TXNRD2主要存在于线粒体，TXNRD3主要存在于睾丸组织[13].

NADPH、硫氧还蛋白(thioredoxin, Trx)和TrxR共同构成硫氧还蛋白系统，其主要通过氧化还原反应传递电子，催化NADPH将Trx上的-S_2还原成(-SH)$_2$，进而维持Trx的还原型，解除机体氧化应激反应，是机体抗氧化应激损伤的主要途径[14,15]. TrxR1和TrxR2可清除细胞质和线粒体内过量的自由基、保护细胞免受氧化应激损伤，而TrxR3主要通过影响结构蛋白中二硫键形成参与精子成熟过程[16]. TrxRs在机体抗氧化防御、氧化还原调节及细胞凋亡等过程中起着重要作用，可作为治疗药物和化合物的靶点.

2.3 碘甲状腺氨酸脱碘酶家族

ID家族是一类包含折叠二聚硫氧还蛋白的硒蛋白，能够催化碘甲状腺氨酸还原性脱碘[17]. 主要分为3种类型：Ⅰ型脱碘酶(DIO1)、Ⅱ型脱碘酶(DIO2)和Ⅲ型脱碘酶(DIO3)，其中DIO1主要存在于肝脏、肾脏和甲状腺中，DIO2存在于垂体、甲状腺、骨骼肌中，DIO3主要存在于大脑皮层和皮肤中[18]. 三者高度保守的活性位点均含有Sec，对维持酶活性至关重要[19].

甲状腺激素(thyroid hormone, TH)是细胞生物学过程的重要调节剂，参与细胞增殖、分化、凋亡和代谢，TH信号传导异常与疾病形成相关. TH在组织的表达通过DIO活性来调节，其中DIO1同时具有外环和内环脱碘作用，可以催化T4转化为T3、T3转化为T2；DIO2主要催化外环脱碘将T4转化为T3；DIO3主要通过内环脱碘抑制T3，将T4或T3转变为无活性的rT3或T2，三者构成甲状腺激素完整的调节系统[20].

2.4 其他硒蛋白

近年来，其他硒蛋白的功能也陆续被证实. 研究报道，SelP是一种硒转运蛋白，在脑和睾丸等多种组织中

维持抗氧化平衡，在硒代谢和抗氧化防御中起着关键作用[21]. SelS参与调节炎症、氧化应激和内质网应激等过程[22]，Sel15、SelK、SelF、SelM、SelN和SelT等均参与内质网氧化还原调节、蛋白质折叠和细胞钙稳态等生理过程，SelH、SelV、SelW、SelO分别在细胞核、生殖细胞、骨骼肌、线粒体中发挥抗氧化作用，SelI还参与生物膜磷脂的合成[23]. 未知硒蛋白的结构和生物学功能也将是今后探索的热点课题.

3 硒蛋白与疾病

3.1 硒蛋白与肿瘤

近年来，在人类健康领域中，学者对硒与癌症的关系研究得较多. 在肿瘤环境中，硒蛋白既可调节细胞氧化还原过程，也可通过氧化应激促进恶性细胞凋亡而呈现抗癌性能. 硒蛋白在预防肿瘤发生、抑制肿瘤生长、促使癌细胞凋亡等方面具有明显的作用，与癌症发生发展密切相关，可能会成为未来临床肿瘤干预的潜在靶点.

研究表明，在高分化肿瘤患者中GPXs酶活性降低，导致抗氧化能力下降，氧化应激增加[24]. 在不同肿瘤类型中GPX3具有双重作用. 一项研究报道，*GPX3*低表达与肺腺癌和胶质瘤发生有关[25]，而在食管鳞状细胞癌，结肠癌等癌症组织中*GPX3*表达升高[26~28]，且*GPX3*高表达与浆液性卵巢腺癌、胃癌、肺鳞状细胞癌等癌症患者预后不良有关[25]. 此外，硒蛋白单核苷酸多态性关联研究表明，*GPX3* rs736775位点多态性与大肠癌和胃癌发病风险相关，*GPX3* rs3805435、rs3828599和rs2070593位点多态性与胃癌风险降低有关，*GPX3* rs3805435和rs3828599位点多态性对分化型甲状腺癌有保护作用，rs8177412位点分化型则与甲状腺癌风险增加有关[25]. 近期研究表明，*GPX1*在肾癌组织中高表达，且与总生存期短、远处转移、淋巴结转移、肿瘤分期呈正相关，*GPX1*表达下调可抑制肾癌细胞的迁移和侵袭[29]. *GPX2*过表达促进了胰腺癌的发生发展，*GPX2*基因沉默可通过下调Wnt通路减轻胰腺癌上皮间充质的转化、侵袭和转移[30]. 此外，*GPX4*和*GPX6*也参与了相关肿瘤的发生发展，且*GPX4*是肿瘤细胞死亡的重要调节因子[31,32].

TRX系统可维持正常细胞氧化还原稳态，抑制肿瘤从生长到侵袭和转移的多个阶段. 研究发现，在肺恶性肿瘤、恶性间皮瘤、肝细胞癌和星形细胞脑肿瘤中*TXNRD1*均高表达，表明*TXNRD1*可促进肿瘤细胞氧化应激水平增加[33]. *TXNRD2*可作为临床治疗多发性骨髓瘤潜在性靶点，其对蛋白酶体依赖的细胞毒性、氧化应激至关重要[34].

脱碘酶对TH的激活或失活作用对调节细胞增殖和分化平衡至关重要. 研究发现，在肾、肺、肝和前列腺癌组织中*DIO1*表达下调，*DIO2*和*DIO3* mRNA水平在垂体肿瘤中明显升高[35]，表明脱碘酶调控下的TH状态在人类肿瘤的发生和发展中起着重要作用. 此外，研究还发现，*SelP*可通过介导基因转录影响肿瘤细胞增殖[36]，*SelP*启动子区甲基化水平可影响机体免疫功能及巨噬细胞活性，进而影响肾肿瘤细胞增殖[37].

3.2 硒蛋白与心血管疾病

硒蛋白在心血管疾病的发生发展过程中扮演重要的角色，主要通过抗氧化应激、抗脂质过氧化和减轻活性氧介导的炎症防治心血管疾病[38,39]. 克山病是膳食硒对人类心血管疾病影响的最有力证据. 研究发现，机体缺硒与充血性心力衰竭有关[40]. 研究表明，硒蛋白GPX1和GPX4表达在心肌缺血/再灌注损伤中发挥重要作用，GPX3还可以通过去除可溶性过氧化产物来抑制血浆LDL的氧化，预防血管炎症和动脉粥样硬化的发生[41].

TXNRD1是一种重要的抗氧化剂，在心肌缺血/再灌注和心力衰竭时具有保护心脏的作用[42]，TXNRD2可保护衰老心肌细胞线粒体的形态和功能完整性，*Txnrd2*缺失导致小鼠扩张型心肌病和围产期死亡[43,44]. 自发性高血压大鼠心力衰竭死亡率与硒摄入量呈负相关，补硒后心肌组织TrxRs活性升高[44]. 研究证实，TRX-1/TrxR1系统通过调节RAS的S-硫醇化等信号介导心脏重塑过程[45].

研究表明，TH水平失调可能导致心血管肥大、心率增加和收缩[41]，急性心肌梗死患者中*DIO1*、*DIO2*基因多态性与其体内TH水平存在关联[46]，上调*DIO2*基因表达可通过激活Akt和p38MAPK信号通路参与扩张型心肌病的心脏重塑[47]. 另有研究表明，肺动脉高压患者SelP水平升高可促进肺动脉高压的发展，SelP缺乏可预测心血管疾病的发病率和死亡率，提示其是一种新的疾病生物标志物和治疗靶点[48,49].

3.3 硒蛋白与关节炎

骨关节炎主要特征是关节软骨进行性变性、软骨

细胞外基质(extracellular matrix, ECM)代谢紊乱和软骨内稳态破坏. 研究报道, 低硒水平是发生骨关节炎的危险因素[50], 骨关节炎患者和小鼠中*GPX1*、*GPX3*和*GPX4*等硒蛋白基因低表达, 硒蛋白水平可通过调节患者体内炎症因子释放延缓疾病发生[51,52]. *DIO2*过表达可显著诱导ECM降解酶, 导致软骨细胞ECM含量降低, 促进骨关节炎的发生, 其可能为骨关节炎治疗的靶点[53,54]. 硒蛋白SNPs等遗传因素被认为是骨关节炎发生的危险因素, 如*DIO2* Thr92Ala和*DIO2* rs12885300多态性可增加骨关节炎发病风险, *DIO3* rs945006基因变异可降低骨关节炎发生[55]. 此外, 骨关节炎患者中*DIO2*、*GPX3*、*TXNRD1*启动子区部分CPG岛甲基化水平降低[56].

3.4 硒蛋白与地方病

大骨节病是一种地方性骨关节疾病, 主要发生在儿童及青少年, 以四肢关节软骨和骺(板)软骨坏死为主要病理改变. 硒蛋白的遗传与表观遗传相互作用与大骨节病的发生和发展有关[57]. 大骨节病生态环境、食物链和病区人群流行病学调查表明, 病区饮用水、土壤和食品中的硒含量均低于非病区[58], 患者血液、尿液和头发中硒含量低于正常人[59], 提示硒在大骨节病发生发展中具有重要作用[52]. Yang等人[60]研究发现, 大骨节病患者的硒蛋白转录谱失调, 其中17个硒蛋白基因(*GPX1*、*GPX2*、*GPX3*、*GPX6*、*DIO1*、*DIO3*、*TXNRD1*、*TXNRD2*、*TXNRD3*、*SPS2*、*SelO*、*SelH*、*SelI*、*SelK*、*SelN*、*SelR*、*SelV*)表达下调, 硒蛋白可能通过影响抗氧化能力参与大骨节病软骨细胞凋亡的发生. 大量研究发现, 硒蛋白基因多态性与大骨节病的发病风险相关, 包括*GPX1* Pro 198Leu、*GPX4*单体型A-T、*DIO2*(rs1352815、rs1388382)、*Sel15* rs5859、*SelS* 105 G>A等, 且*SelS* 105 G>A与PI3K/Akt信号通路上调有关[61~65]. 此外, 大骨节病患者*DIO3*和*GPX3*基因高甲基化和低表达与疾病风险相关, 与大骨节病病情严重程度相关[66,67]. 大骨节病全基因组DNA甲基化谱与mRNA表达谱联合分析表明, 硒化合物代谢通路在大骨节病中具有重要作用[68].

克山病是一种以心肌线粒体损伤为主要特征的地方性心肌病, 其流行的地理环境特点是低硒[69]. 研究表明, 克山病流行区居民血清SelP水平明显低于非流行区[70], 克山病患者中*TrxR1*和*GPX1*基因低表达可降低抗氧化能力, 导致心肌氧化损伤, 其在克山病的发病机制中起重要作用[71]. 另有研究发现, *GPX1* Pro198Leu等位基因携带者体内缺硒, GPX1酶活性低下, 提示低硒和GPX1 198Leu存在协同倍增的交互作用, 从而增加克山病的发病风险[72], 补硒是预防克山病的有效途径[73].

3.5 硒蛋白与新型冠状病毒肺炎

缺硒可破坏机体氧化还原平衡, 减弱宿主抗氧化能力, 使病毒更易复制且毒性增强, 提示硒缺乏与病毒性感染疾病的发生率和病死率有关. 严重急性呼吸综合征冠状病毒2(severe acute respiratory syndrome coronavirus 2, SARS-CoV-2), 又称为新型冠状病毒肺炎(corona virus disease 2019, COVID-19). 近期COVID-19的大流行引发了全球健康危机, 对人类生命健康造成了严重威胁. 研究发现, COVID-19治愈率与硒水平之间存在正相关关系, 区域缺硒可能与COVID-19死亡率升高有关[74]. M^{pro}是SARS-CoV-2的关键酶, 可促进病毒复制复合物的形成[75], GPX1和M^{pro}之间存在关联性[76], 提示硒蛋白GPX1对COVID-19具有重要的保护作用. 因此适当补硒对患有呼吸道病毒感染或营养缺

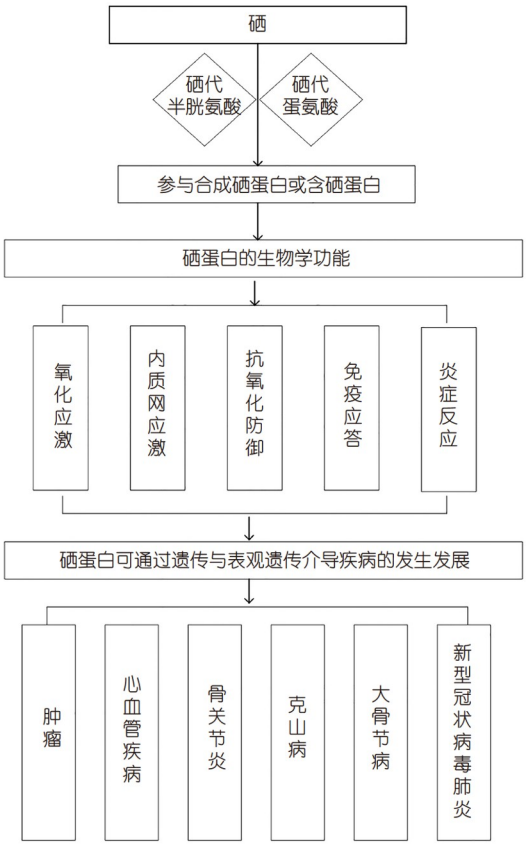

图 1 硒蛋白与人体健康
Figure 1 Selenoprotein and human health

乏的人群具有潜在性益处[77].

4 结语

综上所述，硒蛋白具有抗氧化、抗炎症、抗细胞凋亡，参与调节甲状腺激素代谢，调节机体代谢等功能，其可通过遗传与表观遗传等多种形式参与疾病的发生发展，见图1. 硒蛋白的研究为后续的靶向性治疗疾病提供了新的方向，但由于硒蛋白生物学功能的复杂性和未知性，硒蛋白在抵御疾病、促进人体健康的机制方面仍值得进一步探索和研究.

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Summary for “硒蛋白对人体健康重要作用的研究进展”

Research advance on the important role of selenoprotein in human health

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Selenium (Se) is an essential trace element for animal and human health. Se deficiency and Se excessive intake can lead to severe symptoms and are related to diseases. Se is mainly combined with protein in the form of selenocysteine (Sec) and selenomethionine (Se-Met) in the human body. Generally, proteins formed by incorporating Sec into them are called selenoproteins, while proteins bound in other forms are called Se-containing proteins. Selenoprotein is the main form of Se to exert its biological functions in the human body, and Se deficiency could reduce the content and activity of selenoproteins and disturb the normal physiological function. Researches on the relationship between selenoproteins and human health have received increasing attention, and a comprehensive understanding of the function of selenoproteins is helpful to explain the effects of Se on human health. Although the functions of selenoproteins are not yet fully understood, the critical role of many selenoproteins in human health has been revealed increasingly. So far, 25 kinds of selenoproteins have been found in the human body, and this review focuses on the structure and biological function of glutathione peroxidase (GPX), thioredoxin reductase (TrxR) and iodothyronine deiodinase (ID) families and their relationship with diseases. It shows that selenoproteins such as GPX, TrxR and ID families have biological functions of regulating cell oxidative stress, endoplasmic reticulum stress, antioxidant defense, immune response and inflammatory response. The single nucleotide polymorphism (SNP) and DNA methylation in the promoter region of selenoprotein are related to the risk of diseases. Selenoproteins play a vital role in the pathogenesis and prevention of diseases such as tumors, cardiovascular diseases, osteoarthritis (OA), Keshan disease (KSD), Kashin-Beck disease (KBD), and corona virus disease 2019 (COVID-19) through their genetic and epigenetic forms. This research will provide clues and basis for further revealing the role of Se and selenoprotein in human health and screening to prevent disease targets. However, due to the complexity and unknown biological functions of selenoproteins, the mechanism of selenoproteins in resisting diseases and promoting human health is still worthy of further exploration and research.

selenoprotein, selenium, human health, diseases, biological function

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