中国团队首次揭示介导放射线诱导旁观者效应的关键因子

Chinese Scientists Have Successfully discovered the radiation-induced bystander effects mediated by Cysteine protease cathepsin B for the First Time

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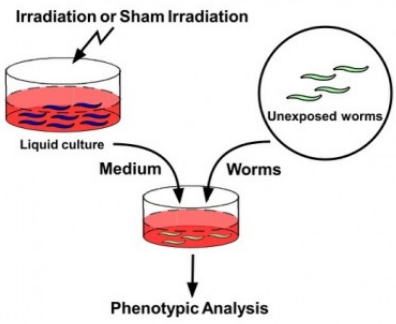
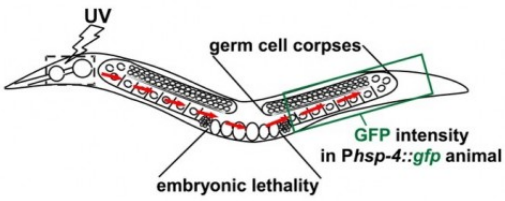
【Nature 系列】7 月 19 日，清华大学生命科学学院薛定研究组在《Nature》期刊发表了题为《组织蛋白酶 B 介导放射线诱导的旁观者效应》 （Cysteine protease cathepsin B mediates radiation-induced bystander effects） 的研究论文， 首次在动物模型上系统地揭示了介导放射线诱导的旁观者效应（radiation-induced bystander effects，RIBE）的关键因子及作用机制。

科学界将未被放射线直接照射的细胞依然受到影响的现象命名为“放射线诱导的旁观者效应”，这一效应会严重干扰癌症放射治疗的效率，并造成脱发，疲劳、皮肤变化等副作用。研究表明，细胞会释放某些因子介导这一效应。但是，由于研究模型与分析方法的局限，在过去的一个世纪里，RIBE 介导因子的身份一直扑朔迷离，这使得它成为放射生物学领域中长期悬而未决的难题。



动物间RIBE模型



体内RIBE模型

现在，薛定研究组利用秀丽线虫建立了动物间和体内两个互补的 RIBE 动物模型（图）以及相关的实验方法，通过富集、生化分馏和质谱手段分析了被照射线虫释放的因子，并最终确认组织蛋白酶 B——一个在进化上高度保守的蛋白酶——是介导 RIBE 效应的关键因子。

同时，他们还发现，放射线照射通过 CEP-1/p53（DNA 损伤修复转录因子和肿瘤抑制基因）提高了组织蛋白酶 B 的转录和翻译，从而促进组织蛋白酶 B 向胞外分泌。分泌的组织蛋白酶 B 作用于未被照射的旁观者细胞，通过同样高度保守的胰岛素样生长因子受体 DAF-2/IGFR 介导的信号通路，抑制细胞凋亡、促进应急反应和细胞增殖，并干扰胚胎和个体发育等一系列效应。

这项工作首次确认了介导 RIBE 的关键因子以及它影响旁观者细胞的作用机理，是放射生物学领域的一项重大进展，并将有利于今后优化癌症放射治疗方法的转化研究 。

Cysteine protease cathepsin B mediates radiation-induced bystander effects

组织蛋白酶 B 介导放射线诱导的旁观者效应

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The radiation-induced bystander effect (RIBE) refers to a unique process in which factors released by irradiated cells or tissues exert effects on other parts of the animal not exposed to radiation, causing genomic instability, stress responses and altered apoptosis or cell proliferation1, 2, 3. Although RIBEs have important implications for radioprotection, radiation safety and radiotherapy, the molecular identities of RIBE factors and their mechanisms of action remain poorly understood. Here we use Caenorhabditis elegans as a model in which to study RIBEs, and identify the cysteine protease CPR-4, a homologue of human cathepsin B, as the first RIBE factor in nematodes, to our knowledge. CPR-4 is secreted from animals irradiated with ultraviolet or ionizing gamma rays, and is the major factor in the conditioned medium that leads to the

inhibition of cell death and increased embryonic lethality in unirradiated animals. Moreover, CPR-4 causes these effects and stress responses at unexposed sites distal to the irradiated tissue. The activity of CPR-4 is regulated by the p53 homologue CEP-1 in response to radiation, and CPR-4 seems to exert RIBEs by acting through the insulin-like growth factor receptor DAF-2. Our study provides crucial insights into RIBEs, and will facilitate the identification of additional RIBE factors and their mechanisms of action.