Melanoma

Major finding: Most cyclobutane-pyrimidine dimers (CPD) form long after UV exposure in a melanin-dependent manner.

Concept: UV-induced reactive species excite melanin to a state with the energy of a UV photon, which can induce CPDs.

Impact: Blockade of "dark CPD" formation by melanin chemiexcitation may reduce levels of UV-induced DNA damage.

CHEMIEXCITATION OF MELANIN GENERATES DNA DAMAGE

UV radiation generates DNA photoproducts called cyclobutane-pyrimidine dimers (CPD) that form almost instantaneously after exposure when a UV photon is directly absorbed by cytosine or thymidine. However, Premi and colleagues made the unexpected observation that melanin pigment–containing melanocytes, but not albino melanocytes, were capable of continuously generating CPDs for several hours after UV exposure ended. These "dark CPDs" accounted for half of all CPDs generated after UV exposure and included cytosine-containing CPDs that underlie UV-signature cytosine-to-thymidine mutations. Reactive oxygen and nitrogen species were required for dark CPD production in melanocytes, with UV exposure promoting the creation of superoxide and nitric oxide to form peroxynitrite, a powerful oxidant capable of exciting electrons to a triplet state with the same high energy of a UV photon. Because triplet states can discharge energy through luminescence, the authors monitored melanocytes for luminescence and found that UV irradiation generated luminescence only in melanin-containing cells. Dark CPD production was triplet state–dependent, and peroxynitrite could create a triplet state in melanin itself, which could then create CPDs in the absence of UV in a cell-free system. Although melanin is cytoplasmic, exposure to UV or peroxynitrite led to rapid solubilization and degradation of melanin polymer into monomers, which are lipophilic and potentially capable of entering the nucleus. Consistent with this possibility, pigmented granules could be observed in the nuclei of melanin-containing, but not albino, melanocytes only after UV exposure. Although further characterization of the process of melanin chemiexcitation is needed, these findings suggest that UV-induced DNA damage can be created long after UV exposure ceases and raise the possibility that interference with melanin chemiexcitation and subsequent dark CPD formation could represent a skin cancer prevention strategy. ■

Premi S, Wallisch S, Mano CM, Weiner AB, Bacchiocchi A, Wakamatsu K, et al. Chemiexcitation of melanin derivatives induces DNA photoproducts long after UV exposure. Science 2015;347:842–7.

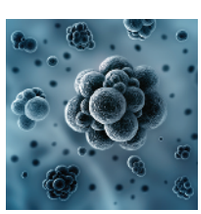
Colorectal Cancer

Major finding: Colorectal cancer metastasis requires both chromosomal instability and driver pathway mutations.

Approach: Human intestinal organoids were engineered to express driver gene mutations using CRISPR-Cas9.

Impact: This system enables identification of molecular lesions that contribute to colorectal carcinogenesis.

AN ENGINEERED CULTURE SYSTEM MODELS COLORECTAL CANCER PROGRESSION



Transformation of normal colon epithelium and progression from adenoma to metastatic colorectal carcinoma has been suggested to occur via loss of the *APC* gene and subsequent mutations in *KRAS*, *SMAD4*, and *TP53* that dysregulate driver pathways and confer a selective growth advantage to intestinal stem cells (ISC). Although these pathways are important regulators of signaling in the ISC niche, their contribution to human colorectal carcinogenesis is unknown. Matano and colleagues developed an epithelial organoid culture system in which driver gene mutations were sequentially introduced into organoids derived from normal human intestinal epithelium using CRISPR-Cas9–mediated genome editing. Isogenic epithelial organoids harboring mutations in *APC*, *KRAS*, *SMAD4*, *TP53*, and *PIK3CA* were selected for by modulating intestinal niche factors required for the growth of normal ISC organoids in culture, thus recapitulating the sequence of mutations in human colorectal cancer progression. Engineered organoids carrying all five mutations (referred to as AKSTP-organoids) grew independently of niche factors. Microarray analysis revealed similar gene signatures in AKSTP-organoids and organoids derived from adenomas, but not those derived from colorectal cancer, suggesting that driver pathway mutations are not sufficient for progression from adenoma to carcinoma. Introduction of driver pathway mutations in engineered AKSTP-organoids enabled tumor formation under the kidney subcapsule of immunodeficient mice and the formation of micrometastases in the spleen; however, these tumors exhibited histologic features of low-grade adenocarcinoma and impaired metastatic colonization of the liver compared with colorectal cancer organoids. Intriguingly, organoids derived from a human adenoma with a chromosomal instability phenotype that were engineered to express driver pathway mutations were capable of metastatic transformation and formed large metastatic tumors. These results suggest that driver pathway mutations contribute to niche-independent stem-cell maintenance, but that other genetic lesions, such as chromosomal instability, are required for colorectal cancer invasion and metastasis. ■

Matano M, Date S, Shimokawa M, Takano A, Fujii M, Ohta Y, et al. Modeling colorectal cancer using CRISPR-Cas9–mediated engineering of human intestinal organoids. Nat Med 2015;21:256–62.

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