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1 Tumors (re)shape biotic interactions:
2 evidence from the freshwater cnidarian
3 *Hydra*

4
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22

23 **ABSTRACT**

24

25 While it is often assumed that oncogenic process in metazoans can influence biotic
26 interactions, empirical evidence for that is lacking. Here, we use the cnidarian *Hydra oligactis*
27 to experimentally explore the consequences of tumor associated phenotypic alterations for
28 the hydra's predation efficiency, the relationship with commensal ciliates and the
29 vulnerability to predators. Unexpectedly, the efficiency of hydra predation on prey was higher
30 in tumorous polyps compared to non-tumorous ones. Commensal ciliates colonized
31 preferentially tumorous hydras than non-tumorous ones, and had a higher replication rate on
32 the former. Finally, in a choice experiment, tumorous hydras were preferentially eaten by a
33 fish predator. This study, for the first time, provides evidence that neoplastic growth has the
34 potential, through effect(s) on host phenotype, to alter biotic interactions within ecosystems
35 and should thus be necessarily taken into account by ecologists.

36

37 Over the last few decades, great attention has been devoted by ecologists to
38 understanding the relationships between biological community dynamics and the functioning
39 of ecosystems¹⁻⁴. It is now clearly established that the outcome of species interactions and
40 their ecosystem consequences are often strongly influenced by variation in the functional
41 traits of the organisms⁵⁻⁸. Factors influencing individual phenotypic variability are numerous,
42 including genetic and epigenetic ones in interaction with external biotic and abiotic variables
43 (e.g., predation, food availability⁷⁻⁹), as well as internal biotic factors associated with the
44 holobiont. For instance, host-microbe interactions are known to influence animal behavior
45 and life-history traits¹⁰⁻¹². Besides, many manipulative parasites have the capacity to alter a
46 broad range of phenotypic traits of their hosts, from color to morphological traits and
47 behavior¹³⁻¹⁶. Because alterations in the phenotype of parasitized hosts can be substantial,
48 it has been argued that manipulated hosts can be ecologically equivalent as new organisms
49 in the ecosystem, involved in novel direct and/or indirect interactions with other species (see
50 also¹⁷⁻¹⁹).

51 In addition to microbiota and parasites, multicellular organisms also evolve with
52 another category of living entity inside their body: the community of neoplastic cells^{20,21}.
53 Neoplastic cell transformation affects most, if not all, multicellular organisms, from hydras to
54 whales²²⁻²⁴. Prior to being, in some cases, fatal for their hosts, tumor development often
55 results in the alteration of phenotypic traits in their hosts, e.g. in morphology^{25,26}, physiology
56²⁷, body odors²⁸, reproductive activities²⁹, as well as social interactions^{30,31}. Despite this
57 large range of phenotypic alterations and the omnipresence of neoplastic processes in the
58 wild, the ecological consequences of neoplastic processes on ecosystems and animals' life
59 histories remain largely unexplored³².

60 To fill this gap, we developed a novel model system, an artificial (tripartite)
61 microcosm, which allows empirically testing whether bearing tumor may have implications
62 for biotic dynamics within ecosystems. The freshwater cnidarian *Hydra oligactis* (further
63 referred to as hydra) is naturally found in aquatic habitats attached to aquatic vegetation or

64 submerged rocks. Within its ecosystem, hydras are involved in a variety of interactions with
65 invertebrates and vertebrates. For instance, they are predators of various zooplankton
66 species or even fish spawn^{33,34}. They can also serve as host for commensal³⁵ or parasite³⁶
67 species. Finally, they can be a prey for fish or mollusks grazing on plants^{37,38}. Domazet-Lošo
68 and co-authors³⁹ have demonstrated that *H. oligactis* polyps can spontaneously develop
69 tumors. These neoplasia not only severely alter the polyp's body shape, but tumor-bearing
70 individuals also show a shift in their microbiota and display a higher number of tentacles
71 (fig1, see also^{39,40}). These tumors reduce the hosts' fitness but rarely kill them, and are
72 vertically transmitted to the buds when polyps reproduce asexually³⁹. The prevalence of
73 tumor-bearing individuals in the natural environment is unknown, but the observation of
74 tumorous hydras in strains derived from wild sampled individuals suggests that
75 susceptibilities to tumor development exist in natural populations (unpublished data, Tökölyi
76 J.). Given the substantial phenotypic differences between healthy and tumorous hydras, we
77 hypothesized that tumorigenesis might influence the biotic relationships involving hydras. To
78 test this hypothesis, we experimentally tested for the first time the consequences of tumor
79 associated phenotypic alterations on three types of biotic interactions: hydras' ability to catch
80 prey, their capacity serving as a host for a commensal ciliate and their vulnerability to
81 predators. Through this pioneer study, we aim to improve our understanding of the impact of
82 tumorigenesis on ecosystem functioning.

83 **Material and methods**

84 Clonal non-tumorous and tumorous individuals *Hydra oligactis* strains (St. Petersburg
85 strains, control and tumorous lineages from the laboratory of Thomas Bosch¹) were used for
86 all experiments³⁹. Polyps were maintained at 18°C in Volvic© water and fed three times per
87 week with freshly hatched *Artemia salina* nauplii according to standard protocols⁴¹. *Artemia*
88 nauplii were obtained by adding 0,5g of eggs microcyst (*Artemia salina*, Planktovie S.A.S.,

¹ Zoological Institute, Christian-Albrechts-University Kiel, Am Botanischen Garten 1–9, D-24118 Kiel, Germany.

89 Marseille, France) in 400ml of seawater prepared with 36 g/L of sea salt (Reef Crystals,
90 Aquarium systems, Sarrebourg, France) and oxygenated with an aquarium pump. After 24 to
91 48 hours of incubation at 30°C, nauplii hatched and were collected with a pipette, rinsed with
92 a filter and suspended in a 200ml beaker of Volvic water.

93 (a) Hydra predation ability

94 For each trial, one hydra was placed in the experimental tank (20 ml well of a 6 well-plate
95 (Thermo Scientific) and left for two minutes of habituation for allowing the polyp to reattach
96 to the substrate. Prey were added at two different prey density levels: In *ad libitum* feeding
97 (by adding 250 µl taken at the bottom of the Artemia beaker, representing more than
98 hundred nauplii) or restricted feeding (by adding 250 µl of Volvic from the upper part of the
99 beaker containing around 10 nauplii in total). The total number of nauplii added in restricted
100 feeding was re-counted at each trial. The predation capacity of hydra was calculated by
101 counting the number of preys captured in their tentacles in 10 minutes under the dissection
102 microscope.

103 (b) Hydra colonization by commensals

104 The ciliates *Kerona pediculus* (named ciliate thereafter) are naturally present on hydra both
105 in the lab and in the wild, and considered as commensals⁴² and hence were used here as a
106 model to test commensal interactions. We collected *K. pediculus* individuals on polyps from
107 an *H. oligactis* C2/7 strain previously sampled in Hungary and maintained in J. Tökölyi's
108 laboratory². Ciliates were taken from C2/7 strain hydra using a one-milliliter pipette tip, under
109 a binocular magnifier, by mildly aspirating the water around the hydra. In a first experiment
110 (free-choice), we introduced one ciliate into the 1.5 ml well of a microplate (12 well-plate,
111 Thermo Scientific) containing one tumorous and one non-tumorous hydra (both free from
112 ciliates). After 4 hours, we recorded on which hydra the ciliate was present. A second
113 experiment consisted in inoculating a single ciliate into a 1.5 ml well containing one hydra,

² Department of Evolutionary Zoology and Human Biology, University of Debrecen, Hungary.

114 tumorous or non-tumorous. We first verified the presence of the ciliate 15h after the
115 inoculation. The number of ciliates on each individual was counted daily over six days. The
116 trials for which ciliates failed to colonize the host were removed.

117 (c) Predation risk on hydra

118 To model the predation interactions, we used Siamese fighting fish (*Betta splendens*) as
119 predator. In the aquarist circle, some fishes are well-known to consume Hydra efficiently⁴³
120 but it is poorly documented in the literature^{37,44}. Fifty adult females were obtained from pet
121 shops (Oxyfish© Verlinghem and Botanic©, Clapiers, France). Each fish was introduced into
122 500ml plastic tanks (16*8,4*6,5cm) in Volvic© water at 25°C at least one hour before the
123 test. A tumorous and a non-tumorous polyps were introduced together in the central hole (5
124 ml) of a standard six well plastic plate for at least ten minutes of acclimation. The plate
125 containing the two polyps was then introduced progressively in the container with the fish
126 and pressed against the wall in front of the camera to allow recording and visualization of
127 each hydra during the test. The upper and open part of the plate was turned inside to let the
128 fish consume the polyps attached in the central well of the plate. Two observers identified
129 precisely the position of each hydra during the test to recognize which one was consumed at
130 each predation event. The trial stopped after the predation of the two hydras or after 45
131 minutes in any case (i.e., no predation or only one specimen predated). Each trial was
132 recorded on a camera (GoPro©).

133 Statistical analysis

134 The effect of the tumorous phenotype on hydra predation was assessed by comparing the
135 total number of Artemia nauplii captured by the two types of hydra (tumorous and non-
136 tumorous). In *ad libitum* condition we used a Poisson generalized linear mixed model
137 (glmm). In restricted feeding condition, we used a binomial glmm taking into account the
138 proportion of artemias consumed over the number introduced initially since small variation
139 can exist between trials. In both analyses we included the hydra type as a fixed effect and

140 the date as a random effect (see model choice in supplementary material). The number of
141 tentacles per polyp of each group was compared using a Wilcoxon test.

142 The proportion of tumorous to non-tumorous hydras colonized by ciliates was compared
143 to the number expected under a no preference hypothesis (50%, binomial test). The
144 verification has been done that there is no effect of the day of measurement using a Fisher
145 exact test and we checked the power of the analysis at a 0.01 alpha risk (see in
146 supplementary material). We used a Poisson glmm to compare the number of ciliates in
147 each group across time with the group as a fixed effect and the individual as a random
148 effect.

149 The proportion of tumorous hydra captured by the predator was compared to the
150 expected number under a random choice, using a binomial test. The verification has been
151 done that there was no effect of the measurement day, using a Fisher exact test. We
152 excluded from the analysis fish that attacked none of the hydras.

153 All analyses were performed using Rstudio (version 1.3). The power of all analyses was
154 measured using the SimR or the MESS package (see supplementary material). When
155 generalized linear random models were used, we specified each family, fixed, random effect
156 choice in the analysis in the supplementary material.

157 **Results**

158 (a) Hydra predation ability

159 Besides carrying conspicuous tumorous budes tumorous *H. oligactis* have been earlier
160 reported to have substantially higher number of tentacles per polyp⁴⁰ (fig1.). The number of
161 tentacles was significantly higher in the tumorous group (9.35 ± 1.14 for tumorous, $5.71 \pm$
162 0.75 for non-tumorous; W -value = 5969, $p < 2.2e-16$). Since the chief function of the
163 tentacles is capturing prey, we hypothesized that the tumorous polyps might have a different
164 predation capacity compared to the healthy polyps. We tested this hypothesis in two feeding
165 experiments - using *ad libitum* and restricted amount of prey. In both feeding conditions,

166 tumorous hydras captured significantly higher number of nauplii than non-tumorous ones (*ad*
167 *libitum*: fig2a., Incidence ratio rates (IRR) = 1.31 ± 0.07 ; $Z= 5.245$; $df= 81$, $p<0.001$);
168 restricted feeding conditions: fig2b., Odds ratio (OR) = 1.54 ± 0.14 ; $Z=3.091$; $df=80$;
169 $p=0.002$). These results suggest that tumorous phenotype in hydra is associated with altered
170 interactions with its prey.

171 (b) Hydra colonization by commensals

172 Because host surface serves as a habitat for epibiont species, and that the body of tumorous
173 hydras is severely modified in size and shape, we predicted that the tumorous phenotype
174 may influence the colonization preference and/or dynamics of the commensal epibiont - the
175 ciliate *K. pediculus*. When given the choice between a tumorous and a non-tumorous hydra,
176 the ciliates colonized preferentially the tumorous one (fig3a., $81\% \pm 13\%$, $p = 6.877e-05$,
177 $\alpha=0.01$, binomial exact test, $n=42$), without any effect of the day of measurement ($p =$
178 0.1081 , $\alpha=0.01$, Fisher exact test, $n=42$). Of the 36 individuals inoculated with ciliates,
179 24 non-tumorous and 33 tumorous were colonized successfully by ciliates. Long-term
180 observation of the colonization dynamics uncovered that the number of ciliates on hydra
181 increased faster over time and reached higher densities on tumorous hydra than on the non-
182 tumorous ones (fig3b., $IRR=1.19$; $Z= 3.208$; $df= 337$, $p= 0.001$). These results suggest that
183 tumorous phenotype in hydra is associated with altered interactions with commensal
184 species.

185 (c) Predation risk on hydra

186 Given that tumorous and non-tumorous hydras do not have the same size/morphology, we
187 predicted that they may experience a different predation risk by visually hunting predators.
188 To test this hypothesis, we used Siamese fish as predators. They ate hydras in 37 out of 51
189 trials and the first hydra consumed was significantly more often the tumorous one (fig4a., i.e.
190 73% of cases, 27 times over 37 trials, $p = 0.008$, binomial exact test). Nine fish preyed only
191 on the tumorous hydra and none of them preyed only the non-tumorous one (fig4b.). There

192 was no influence of the measurement day ($p= 0.650$, Fisher exact test, $n=37$). When the first
193 hydra consumed was a non-tumorous one, the time needed to observe the second predation
194 event was significantly shorter than when the first hydra captured was the tumorous one
195 (fig4c., 715 ± 738 seconds vs. 55 ± 98.3 seconds; $Z=-4.632$, $p=3.62e-06$, $df=26$). Although
196 this shorter delay could indicate that satiation is more rapidly reached when the first prey
197 was the tumorous individual, our findings are overall in accordance with the hypothesis that
198 tumorous polyps are more detectable than non-tumorous ones.

199 **Discussion**

200 Ecological implications of oncogenic processes, while theoretically important in ecosystem
201 functioning⁴⁵, have never been studied experimentally until now. This study provides
202 empirical evidence for the first time for the hypothesis that the phenotypic consequences
203 associated with the presence of tumor(s) in an organism reshape, qualitatively and/or
204 quantitatively, various types of biotic interactions. We found that (i) the predation
205 performance of tumorous hydras was increased compared to non-tumorous ones, (ii) the
206 tumoral phenotype is more often colonized by a ciliate and with a faster colonization and (iii)
207 tumorous hydras were preferentially eaten by predatory fish. Although tumorous and non-
208 tumorous hydras used in our experiments differ in the presence of tumors and their
209 phenotypic consequences, as well as their microbiota⁴⁰, they originate from the same
210 ancestral polyp and are genetically identical (clonal). Therefore, the alterations of biotic
211 interactions reported here are most likely caused by the phenotypic alterations induced by
212 the tumors (i.e. non-tumorous hydra being here a perfect control).

213 The significantly higher ability of tumorous hydras to capture prey may first appear
214 counterintuitive given that neoplasms are usually associated to reduced host performances
215^{46,47}. The most parsimonious explanation here is that this higher performance is due to the
216 increased number of tentacles in tumor-bearing hydras compared to non-tumorous ones
217 (see also³⁹). Precise causes behind this novel phenotype are unclear and could have

218 different origins since it could benefit the host (e.g. compensatory mechanisms, see for
219 instance ⁴⁸), the tumor (e.g. host manipulation, see for instance ⁴⁹) or be beneficial for both
220 the host and the tumor (see for instance ⁵⁰). Deciphering the molecular cross-talk between
221 the host and the tumor during the window when additional tentacles are growing could help
222 to clarify this point (see for instance ⁵¹). Further experiments estimating fitness benefits for
223 the host and the tumor would be required to distinguish between these possibilities. Also,
224 given that microbiota is altered in the tumorous polyps, and that the microbiota alters the
225 behavior of hydras⁵², we cannot exclude that a modified neuronal activity and feeding
226 behavior might be responsible for the more efficient predation of tumorous polyps. We
227 particularly emphasize here that the effect of higher predation efficiency was observed in
228 both feeding conditions, ad libitum and restricted feeding, whereby the limited food supply is
229 likely the more natural condition for hydra⁵⁴. In any case, these results suggest that the level
230 of resources could influence the coexistence between tumorous and non-tumorous
231 individuals in a non-expected manner. Indeed, while it is intuitively logic that tumorous
232 individuals, already weakened by the presence of tumor, would suffer more from a lack or
233 from scarcity of prey than non-tumorous ones, our results conversely suggest that their
234 persistence could be facilitated in poor habitats.

235 The higher preference of ciliates for tumor-bearing individuals, as well as their faster
236 replication rate on them compared to non-tumorous ones, may indicate that the formers offer
237 a larger living surface and/or more resources for epibiont organisms. Precise mechanisms
238 operating here remain however to be determined, at least four hypotheses could be tested.
239 (i) Ciliates prefer chemical cues specifically produced by tumor-bearing individuals, (ii)
240 tumor-bearing individuals might be more easily detected or encountered by actively
241 searching ciliates because of their bigger size, their higher number of tentacles and/or a
242 different behavior associated with tumors, (iii) tumorous hydras might lack some defenses
243 against ciliates and are then more vulnerable to the opportunistic colonization, (iv) tumorous
244 hydras might harbor more bacteria and/or release more feeding byproducts useful for ciliates

245 due to their altered feeding behavior. The commensal role itself of this ciliate remains
246 however to be explored^{35,53,55-57}. For instance, the presence of a high number of ciliates
247 seems to be associated with an increased budding rate in *H. oligactis*, but the causes of this
248 phenomenon are not well understood³⁵. Thus, we cannot exclude that the commensal nature
249 of the interaction between this ciliate and the hydra is not stable and varies with different
250 parameters including the density on hydra. Further explorations of the impact of ciliates'
251 density on the fitness (e.g. budding rate, survival) of tumorous and non-tumorous hydras
252 could help us to understand the costs and/or the benefits of these commensals for tumorous
253 and non-tumorous hydras.

254 The higher predation risk of tumor-bearing hydra could be ascribed to both visual and
255 chemical cues, since the fish species used here is able to exploit both, at least in sexual
256 selection and competition contexts⁵⁸⁻⁶⁰. However, given that this fish is mostly a visually
257 hunting predator^{61,62} and from our observations during the experiments, we favor the first
258 hypothesis, i.e. that they detect and capture in priority bigger (tumorous) preys. The
259 respective role of the abnormal neoplastic mass and/or of the higher number of tentacles in
260 enhancing the hydra detectability could be tested in the future by removing some tentacles
261 from tumor-bearing individuals, and/or by grafting the upper part of tumorous hydras on non-
262 tumorous ones and vice versa (see for instance⁶³). In addition, further experiments should
263 also focus on the possible role of the behavioral differences between tumorous and non-
264 tumorous hydras. For instance, tumorous polyps do not contract spontaneously and their
265 induced contractility is compromised. Therefore, they potentially could not retract themselves
266 in case of attack and/or have a lower ability to detect predators (hydras are light sensitive
267 and can detect shadows from the fish⁶⁴).

268 Because this study was experimental and the prevalence of tumor-bearing
269 individuals is unknown in the field, the extent to which these findings illustrate processes
270 occurring in the wild remains to be determined. We have developed here a unique

271 experimental pattern, with tripartite microcosm composed of two interacting organism with,
272 one containing tumoral cells considered as a third living entity impacting the interaction. It
273 allows assessing the impact of tumor burden onto multiple biotic interactions within an
274 ecosystem. Moreover, it can provide new insights for a mechanistic understanding of these
275 dynamics. The simplicity of the system and its accessibility offers unlimited perspective for
276 ecological, behavioral or even biochemical studies.

277 Beyond the present demonstration that the tumorigenesis has the potential to alter
278 biotic interactions, further experiments manipulating in microcosms the frequency of tumor-
279 bearing individuals in *Hydra oligactis* populations would be necessary to simulate the
280 possible cascade effects on the whole aquatic community. As suggested above, these
281 experiments should also test if the influence of tumors in biotic interactions depends on the
282 phenotypic variation already existing in tumor-free individuals, especially natural size
283 variability of non-tumorous hydra. Our experiments also uncovered a truly surprising
284 phenomenon: bearing tumor may appear advantageous in particular conditions. The
285 evolutionary significance of this principle and its impact onto the species' life history may be
286 also studied in long-term experiments.

287 The results we presented here suggests that neoplastic processes in biological
288 communities should be fully considered by ecologists to understand and predict the
289 evolutionary ecology of species interactions, as well as their consequences on ecosystem
290 functioning. This research direction is likely to become crucial in the future given that
291 ecosystems are increasingly exposed to oncogenic pollution resulting from anthropic
292 activities³².

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301 Ethic statement:

302 All experimental animals were treated in accordance with French and European Union
303 regulations (directive 2010/63/UE). All the behavioural observations were included in the
304 project authorization APAFIS: 29961. No fishes were injured or killed during the
305 experiments.

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473 Legend of figures

474 Figure 1: Phenotypic differences of non-tumorous and tumorous hydras

475 The non-tumorous hydra is on the left and the tumorous one on the right. We can notice an increased body size and number of
476 tentacles.

477 Figure 2: Tumorous hydras have higher predation abilities

478 The number of prey captured per hydra (a.) in *ad libitum* and in restricted feeding (b.). The proportion of prey captured per
479 hydra in restricted feeding were counted during ten minutes. Boxplots represent the first, median and third quartiles on the 95%
480 extent. A point represents each measurement with the non-tumorous group in green and the tumorous in red. (c.) Pictures of
481 tumorous and non-tumorous hydras capturing prey.

482 Figure 3: Ciliates established easier on tumorous hydras than on non-tumorous ones.

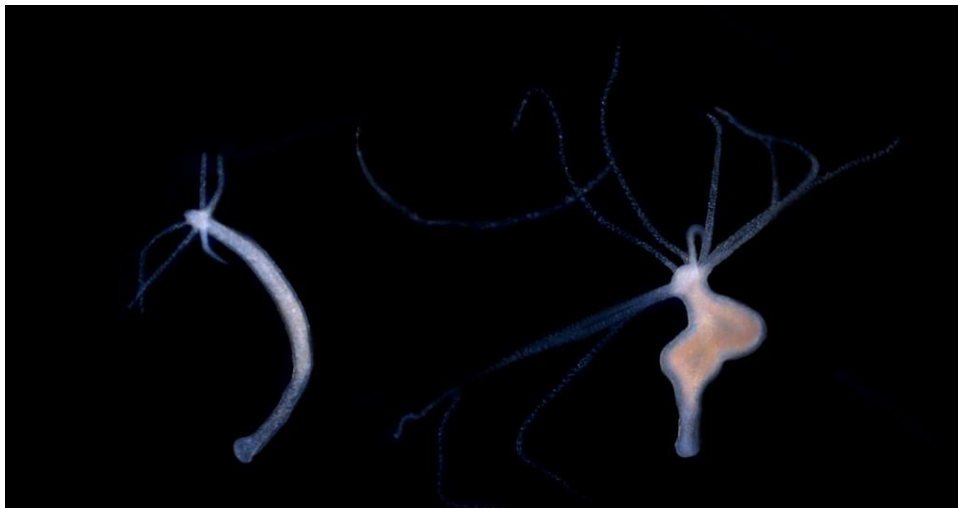
483 (a.) Five hours after the introduction of a ciliate into an experimental tank containing both hydra type, we found 81% of the
484 ciliates attaches to the tumoral host instead of the non-tumoral one. (b.) After the introductions of one ciliate into the well of a
485 tumoral or a non-tumoral individual, we counted daily the number of ciliates per hydra. Each point represents the number of
486 ciliates measured on a given day; the size of the point depends on the number of hydras recorded at this measurement. The
487 black line represents the average value predicted by the model and the colored areas the confidence interval at 95% predicted
488 by the model. In green, on the left, the non-tumorous group on the left and in red, on the right, the tumorous group on the right
489 in red. (c.) Pictures of eleven ciliates attached to a hydra at x20 and zoomed picture of one ciliate on a hydra.

490 Figure 4: Tumorous hydras have a higher predation risk by fish than non-tumorous 491 ones

492 (a.) The histogram represents the number of fish that consumed first the tumoral (in red), the non-tumoral (in green) or none of
493 the hydra during the test (in grey). Among the 37 trials which fish consume a first hydra, the pie plots represent the proportion of
494 fish that consumed the second one. The color of the section corresponds the type of the remaining hydra; in grey if the second
495 hydra consumed is non-tumoral, in red if the second hydra consumed is tumoral and in grey if the fish did not consume the
496 second hydra. (c.) A point represents the time required to the fish to consume the second hydra after the first one, on the left
497 when the remaining prey is non-tumorous (in green), on the right when it is a tumorous (in red). (d.) Pictures of two hydras, a
498 tumoral and a non-tumoral in a plastic well plate. The fish consumed the tumoral, and then, only the non-tumoral remain visible
499 on the last picture. These illustrative pictures were taken during a session separate from the experiments.

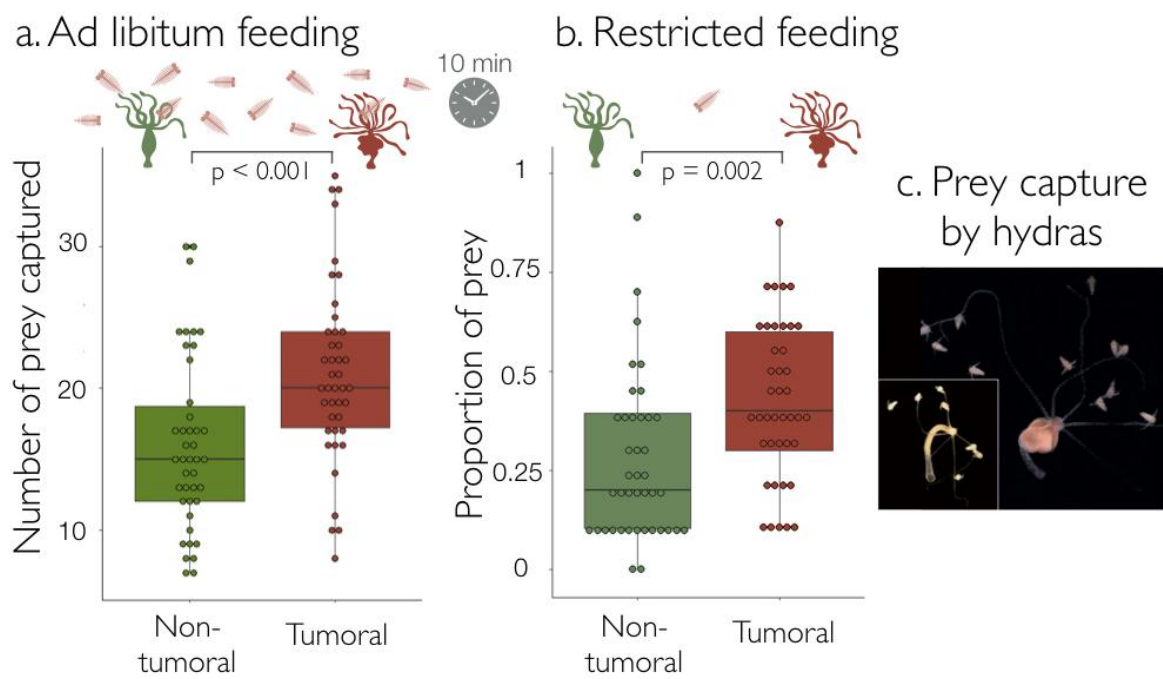
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501 **Figures**



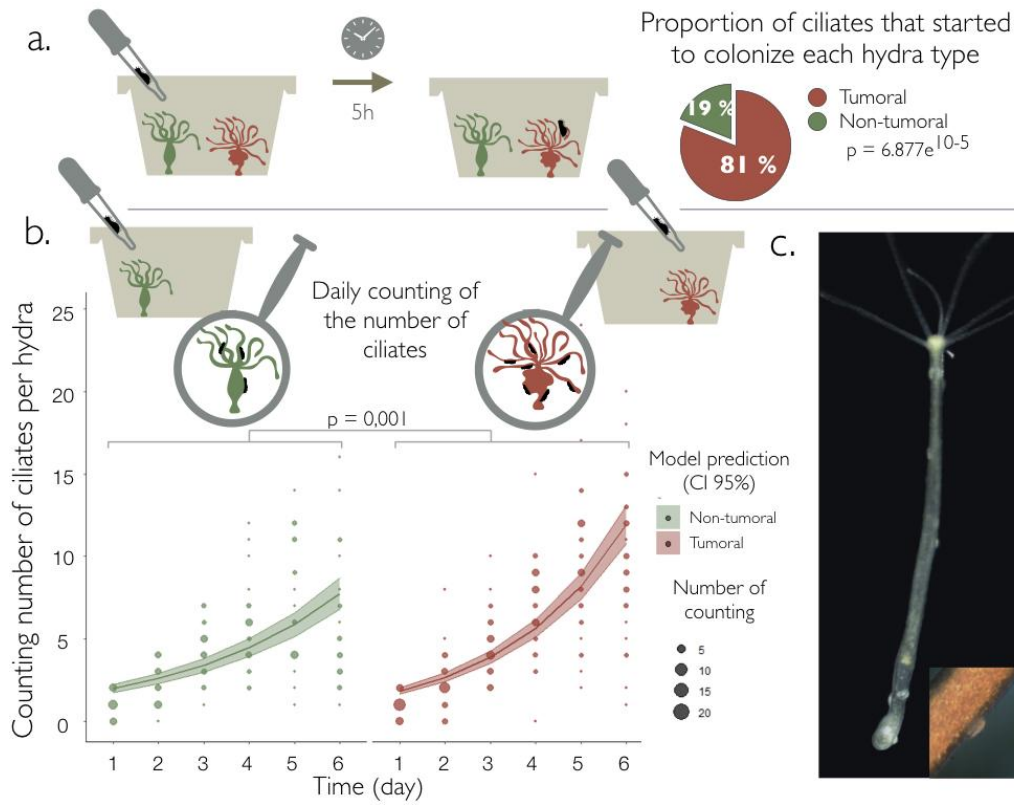
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503 **Figure 1. Phenotypic differences of non-tumorous and tumorous hydras**



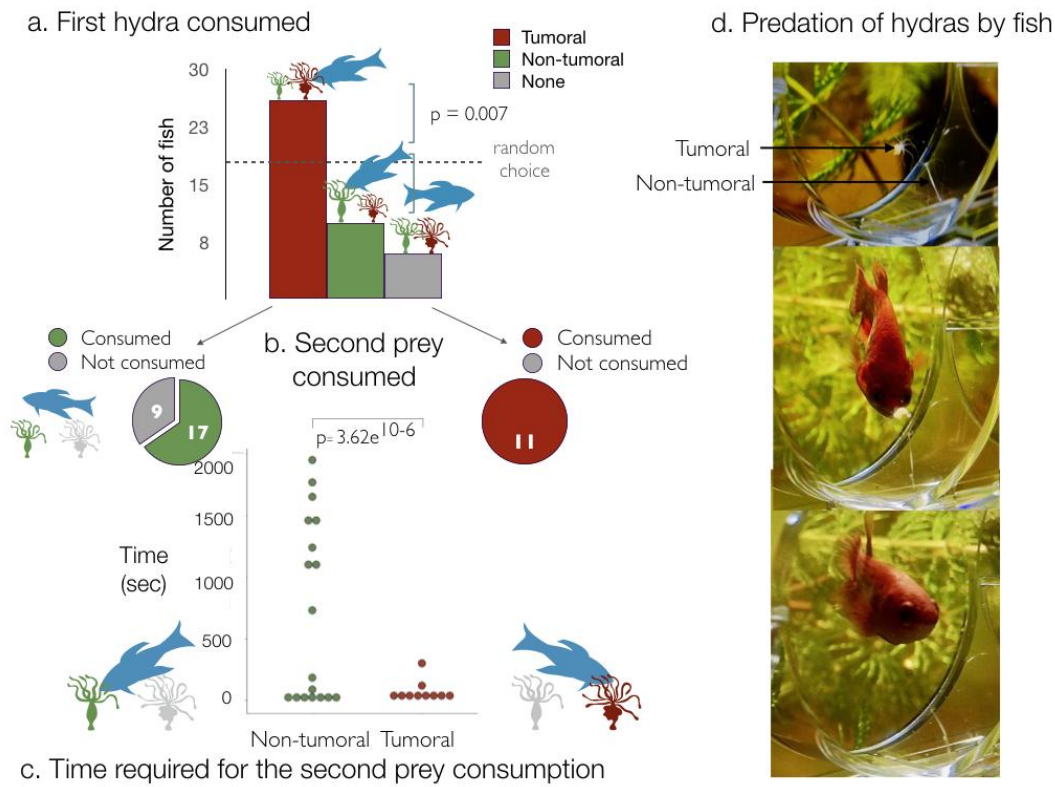
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505 **Figure 2. Tumorous hydras have higher predation abilities**



506

507 **Figure 3. Ciliates established easier on tumorous hydras than on non-tumorous ones.**



508

509 **Figure 4. Tumorous hydras have a higher predation risk by fish than non-tumorous**
510 **ones**